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Drinking Water Criteria Document for Pentachlorophenol

Environmental Criteria and Assessment Office
Cincinnati, OH

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The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on pentachlorophenol. This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of pentachlorophenol
- Toxicokinetics and human exposure to pentachlorophenol
- Health Effects of pentachlorophenol in humans and animals
- Mechanisms of toxicity of pentachlorophenol
- Quantification of toxicological effects of pentachlorophenol

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Prepared for

OFFICE OF DRINKING WATER

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I. SUMMARY

Pentachlorophenol (molecular weight, 266.34) forms colorless crystals with a definite phenolic odor. This compound is stable in aqueous solution with a solubility of 20 mg/ℓ at 30°C, though microbial and photochemical degradation may occur. Although pentachlorophenol may be obtained as a pure compound, technical and commercial grades are contaminated with a number of highly toxic impurities, including chlorinated dibenzo-p-dioxins, dibenzofurans and hexachlorobenzene.

Pentachlorophenol is rapidly absorbed following oral, dermal or inhalation exposure. The major tissue depots of pentachlorophenol are the liver, kidneys, brain, spleen and fat. The tissue/plasma concentration ratio is less than would be expected when there is extensive protein binding in the plasma. Following a single dose, pentachlorophenol is rapidly excreted with a half-life of ~10 hours, indicating that there should be little tendency for pentachlorophenol to accumulate in the body. During chronic exposure, however, the excretion kinetics appear to be altered, resulting in a biological half-life of ~20 days. Therefore, blood levels during chronic exposure are generally higher than would be predicted from single-dose models. At the same time, a tolerance to the toxic effects of pentachlorophenol appears to develop, at least in rats. Blood levels 2-5 times those observed following a single lethal dose may be reached before death occurs. The major route of excretion is the urine, with lesser amounts being excreted in the feces and only traces appearing as CO_2 in the expired air.

Signs of toxicity in animals following either acute or chronic oral exposure are similar. There is an initial rise in body temperature and respiration rate, with respiration becoming slower and dyspneic as coma develops. Death is characterized by cardiac and muscular collapse with terminal asphyxial convulsions. Following dermal exposure, the signs of toxicity are similar to those following oral exposure with the addition of local dermal irritation at the site of application. Rigor mortis occurs quickly and is unusually pronounced. Liver and kidney involvement is often noted in cases of chronic poisoning. Reported oral LD_{50}s range from 27 to >300 mg/kg bw; however, the lower values probably reflect contamination with the highly toxic chlorinated dibenzo-p-dioxins and dibenzofurans.

Pentachlorophenol is not a demonstrated carcinogen and is, at most, only marginally mutagenic. No reported study has related treatment with purified pentachlorophenol to tumor development, though one study did report an increase in hepatic tumors in rats following treatment with technical grade pentachlorophenol.

Pentachlorophenol is fetotoxic and has adverse effects on reproduction in laboratory rats. Treatment with pentachlorophenol results in increases in resorptions and alterations in the sex ratio of rat pups with males predominating in the surviving pups. A number of skeletal anomalies have been reported; however, the investigators considered these to be toxic rather than teratogenic effects. In rats, the most sensitive period occurs on days 8-10 of gestation. Little pentachlorophenol reaches the fetus once the chorioallantoic placenta has formed.

In humans, local irritation, allergic responses and systemic effects have been reported. Pentachlorophenol poisoning is characterized by a profuse sweating, often accompanied by fever, weight loss and gastrointestinal complaints.

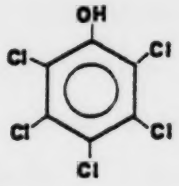
The major mechanism of pentachlorophenol toxicity is believed to be the uncoupling of cellular oxidation and phosphorylation. This results in an increase in the basic metabolic rate, which may account for many of the symptoms observed in cases of pentachlorophenol poisoning. Pentachlorophenol may affect the toxicity of other compounds by a variety of mechanisms. The best characterized of these involve alterations of metabolism, either through induction of microsomal enzymes or inhibition of sulfation.

Based on the reported toxicities of pentachlorophenol in experimental animals, 1-day, 10-day and lifetime health advisories were derived. The resulting values for a 1-day health advisory are 3.5 mg/ℓ for a 70 kg adult and 1.0 mg/ℓ for a 10 kg child. The 10-day health advisories of 1.1 mg/ℓ for a 70 kg adult and 0.30 mg/ℓ for a 10 kg child are only slightly lower than the 1-day health advisories, and the lifetime adjusted acceptable daily intake (AADI) is the same as the adult 10-day health advisory. Water concentrations approaching the health advisories for adults are likely to be unacceptable, due to organoleptic considerations.

II. GENERAL INFORMATION AND PROPERTIES

Structure and Identification

Pentachlorophenol is also known as PCP and pentachlorohydroxybenzene and is available in a variety of products including Penta, Santophen 20, Dowicide 7, Chlorophen, Penchloro, Sinituho, Weedone, Santobrite, EP 30, Liropren, Lauxtol, Fungifen, Durotox, Thompson's Wood Fix, Term-1-Trol, Permite, Penta-Kil, Pentasol, Penwar, Perotox, Permacide, Permagard, Permatox and Chem-tol. The structure of pentachlorophenol is as follows:



Molecular formula: C_6Cl_5OH

Molecular weight: 266.34

The Chemical Abstracts Service (CAS) registry number for this compound is 87-86-5 and the Registry of Toxic Effects of Chemical Substances (RTECS) number is SM6300000.

Chemical and Physical Properties

The physical properties of pentachlorophenol are summarized in Table II-1. The commercial product exists as white to light yellow beads, powder or crystals and has a characteristic strong odor when hot. In the pure form, pentachlorophenol forms colorless crystals with a phenolic odor (BCPC, 1977).

TABLE II-1

Physical Properties of Pentachlorophenol

Property	Value	Reference
Molecular weight	266.34	CRC, 1973
Boiling point	309-310°C	CRC, 1973
Melting point	191°C (anhydrous)	CRC, 1973
Vapor pressure	0.00011 mm Hg at 20°C	Verschueren, 1983
Solubility[a]	14 mg/ℓ water at 20°C	Verschueren, 1983
	5 mg/ℓ water at 0°C	Verschueren, 1983
	very soluble in ethanol and ether	CRC, 1973
	soluble in hot benzene	CRC, 1973
	limited solubility in carbon tetrachloride	BCPC, 1977
	slightly soluble in petroleum ether	BCPC, 1977
Log octanol/water partition coefficient	5.86	Hansch and Leo, 1979
Specific gravity	1.978_4^{22}	CRC, 1973
λmax (log ε)[b]	300.5 (3.4)	CRC, 1973
λmax (log ε)[b]	308 (3.4)	CRC, 1973
pKa	4.74	Drahonovsky and Vacek, 1971

[a]Sodium pentachlorophenate is highly soluble in water.

[b]In ethanol

Conversion factors for air concentrations: 1 ppm = 10.9 mg/m³
1 mg/m³ = 0.092 ppm

Pentachlorophenol photodegrades rapidly in both laboratory and rice field water with a half-life of 48 hours in a borosilicate glass flask irradiated with sunlight at pH 7.3 (Wong and Crosby, 1981). At pH 7.3 pentachlorophenol is present as the anion; at pH 3.3 the authors reported a much longer half-life (>90 hours). In natural systems, the half-life was longer due to light intensity attenuation with depth (Burns et al., 1981). Products of the photolysis were found to include 2,3,4,6- and 2,3,5,6-tetrachlorophenol, tetrachlororesorcinol, tetrachlorocatechol, 2,3-dichloromaleic acid, chloropropionic acid, 4,5-dichloro-1,3-cyclopentanedione, tetrachloro-1,4-benzoquinone and 3,6-dichloro-2,5-dihydroxyl,4-benzoquinone. When high concentrations of pentachlorophenol were irradiated, small quantities of octachlorodibenzo-p-dioxin were formed. Wong and Crosby (1981) also analyzed a stream near a wood treatment plant and found, in addition to pentachlorophenol, some 2,3,4,6-tetrachlorophenol and a dichlorophenol but no 2,3-dichloromaleic acid, a principal degradation product. Pierce and Victor (1978) also reported finding tetrachlorophenols after a pentachlorophenol spill.

Biodegradation rates for pentachlorophenol vary considerably (Alexander and Aleem, 1961; Tabak et al., 1981; Baker et al., 1980; Rott et al., 1982; Korte and Klein, 1982; Schefer and Waelchli, 1980). This marked variation appears to be related to the initial concentration of the phenol, with higher levels apparently being toxic to the microorganisms. Alexander and Aleem (1961) reported 100% removal of a 50 µg/mℓ (ppm) solution of pentachlorophenol in 72 days using a soil suspension. Tabak et al. (1981) used a sewage seed and reported 100% degradation in 21 days at 5 µg/mℓ pentachlorophenol while at 10 µg/mℓ, 28 days were required to achieve a

99% removal. Baker et al. (1980) reported only a 1% removal of pentachlorophenol in 40 days at 100 µg/mℓ concentration from a stream water at 20°C. When sediment was added, a 29% removal was achieved in 30 days.

Pentachlorophenol has a pK_a of 4.74 and, consequently, exists as the anion in most environmental surface waters (Callahan et al., 1979). As such, the log octanol/water partition coefficient (log P_{ow}) reported for the parent compound (5.86) can not be an indicator of the sorption potential of pentachlorophenol in the environment, since the anion is more soluble in water than the parent compound. No log P_{ow} value could be located in the available literature for the anion. Hiatt et al. (1960) reported that pentachlorophenol did not sorb to neutral soils but did sorb to acidic soils. The most sensitive parameter in controlling the sorption of pentachlorophenol is pH, while soil organic matter determines how much compound will sorb (Choi and Aomine, 1974). Thus, in organic rich acidic sediments, pentachlorophenol will be expected to sorb, while in slightly acidic, neutral or basic sediments, sorption will not be expected. Supporting this conclusion are the reports of Pierce (1978) and Pierce and Victor (1978), who followed the fate of two accidental spills of pentachlorophenol in a lake. Pentachlorophenol was found to sorb to leaf litter, which appeared to control its transport throughout the lake.

Pentachlorophenol has been detected in many effluent streams and in some finished drinking water (Shackelford and Keith, 1976; Buhler et al., 1973). Buhler et al. (1973) studied pentachlorophenol removal from sewage treatment plants by monitoring both the influent and effluent. They reported an aver-

age 4-28% removal. The authors also reported that pentachlorophenol concentrations in the Willamette River entering the Corvallis Taylor water treatment plant were 0.10-0.70 ppb; the plant removed ~60% of the pentachlorophenol, leaving ~40% in the finished drinking water. Wegman and Hofstee (1979) reported detecting pentachlorophenol in all 206 samples taken between 1976 and 1977 at six sites along the Rhine River and tributaries in the Netherlands. Concentrations averaged 1.13 µg/ℓ (ppb), with the highest concentration reaching 11 µg/ℓ. Between 1979 and 1980, sediment samples were taken from 35 sites, many of which were along the Rhine River and tributaries (Wegman and van den Broek, 1983). Pentachlorophenol was found in all samples with the highest levels in the Nieuwe Maas River near Rotterdam, a heavily industrialized area. Where both surface water and sediment were analyzed at the same time, sediment concentrations of pentachlorophenol were found to be 20 times higher than the water. Concentration factors for other chlorophenols were higher, 2,4-dichlorophenol being the highest at 440. No information was provided on the composition of the sediments (i.e., percent organic matter, pH) and it is not known if the sediments provided a sink for pentachlorophenol, slowly partitioning it into the water. By contrast, Wong and Crosby (1981) analyzed surface ponds and agricultural drainage water near a wood-treatment facility and found pentachlorophenol concentrations between 1 and 800 µg/ℓ (average 227). Pentachlorophenol in well water in the area ranged between <1 and 50 µg/ℓ. Pentachlorophenol concentrations downstream in the Sacramento River water were <1 µg/ℓ.

Pentachlorophenol is synthesized by the direct chlorination of phenol and sold as the free phenol or as the sodium salt, sodium pentachlorophenate. Commercial pentachlorophenol varies in purity with pentachlorophenol

itself accounting for ~88-91% of the product. Analyses for two commercial (Dow) and one "purified" pentachlorophenol products are listed in Table II-2. No analyses of pentachlorophenol produced in the 1950s or earlier were found in the available literature. Manufacturing processes up to the middle 1950s were apparently based on a 1938 patent (Golumbic, 1953); manufacturing processes today appear to be based on patents issued in the late 1950s and early 1960s and purification methods patented in the 1970s (Freiter, 1979), so that the composition of pentachlorophenol may well have changed with time. In addition, pentachlorophenol appears to be a substantial component of commercial tetrachlorophenol (Schwetz et al., 1974a).

Summary

Pure pentachlorophenol has a molecular weight of 266.34, is a solid at ambient temperatures and forms colorless crystals with a phenolic odor. It has a water solubility of 14 mg/ℓ at 20°C and a pK_a of 4.74. Pentachlorophenol is stable in aqueous solution in the dark; however, photochemical (Wong and Crosby, 1981) and some microbial degradation (Alexander and Aleem, 1961; Baker et al., 1980; Tabak et al., 1981) will result in some depletion in surface waters. It has been found in finished drinking water and is known to persist in some surface waters, while degradation is apparent in others (Wegman and Hofstee, 1979; Wegman and van den Broek, 1983; Wong and Crosby, 1981).

TABLE II-2

Commercial Pentachlorophenol Impurities

	Dow Lot No. MM06210-9822[a]	Purified Ref. No. 29-91-1[a]	Unspecified Commercial[b]
Phenolics (%)			
Pentachlorophenol	88.4	98 +	90.4 ± 1.0
Tetrachlorophenol	4.4	0.27	10.4 ± 0.2
Trichlorophenol	<0.1	0.05	<0.1
Higher chlorinated phenoxyphenols	6.2	0.5	NR
Nonphenolics (ppm)			
2,3,7,8-Tetrachlorodibenzo-p-dioxin	<0.05	<0.05	<0.05
Hexachlorodibenzo-p-dioxin	4	<0.5	1.0 ± 0.1
Heptachlorodibenzo-p-dioxin	125	<0.5	6.5 ± 1.0
Octachlorodibenzo-p-dioxin	2500	<1.0	15.0 ± 3.0
Hexachlorodibenzofuran	30	<0.5	3.4 ± 0.4
Heptachlorodibenzofuran	80	<0.5	1.8 ± 0.3
Octachlorodibenzofuran	80	<0.5	<1
Hexachlorobenzene	NR	NR	400 ± 40

[a]Schwetz et al., 1974b

[b]Schwetz et al., 1978

NR = Not reported

III. TOXICOKINETICS

Information on the toxicokinetics of pentachlorophenol in humans and animals after single doses is summarized in Table III-1. The available data indicate that pentachlorophenol is rapidly absorbed following acute oral, dermal or inhalation exposure, and then excreted over the next 3-6 days. The excretion rate may be reduced following chronic exposure.

Absorption

Oral Exposure. Meerman et al. (1983) examined the uptake of pentachlorophenol and sodium pentachlorophenol by male Wistar rats (100-120 g) after ad libitum exposures for 1 week in the diet or drinking water. Exposure levels, resultant plasma concentrations and other experimental details are presented in Table III-2. The investigators noted wide diurnal variations in plasma levels of pentachlorophenol associated with changes in feeding activity, with the highest plasma concentrations occurring during the night. Based on an analysis of plasma levels during a 24-hour period as well as toxicokinetic parameters obtained from a separate study using intravenous (i.v.) administration (Excretion Section), the investigators calculated that virtually all of the administered pentachlorophenol was absorbed from drinking water. Braun and Sauerhoff (1976) and Braun et al. (1977) compared the toxicokinetics of pentachlorophenol in rhesus monkeys and Sprague-Dawley rats. Groups of six rats, three of each sex, received a single gavage dose of 10 or 100 mg [^{14}C]pentachlorophenol/kg bw in 1 mℓ corn oil. Three male and three female monkeys, Macaca mulatta, weighing 3.3-4.9 kg received a single gavage dose of 10 mg/kg bw in 10 mℓ corn oil. In both species, pentachlorophenol was rapidly absorbed, with peak plasma levels occurring in 12-24 hours in the monkeys and 4-6 hours in the rats.

TABLE III-1

Pentachlorophenol Toxicokinetics in Mammals After Single Doses[a]

Species	Sex	Route (vehicle)	Dose (mg/kg)	Peak Blood Level (ppm)	Time to Peak Level (hours)	Half-Life (hours)	Excretion	Comments	Reference
Man	M	oral (NR)	0.1	0.248	4	30.2 (plasma)	Peak at 42 hours; half-life for PCP was 33 hours; half-life for PCP-glucuronide was 12.7 hours	74% in urine as PCP; 12% in urine as PCP-glucuronide; 4% in feces as PCP and PCP-glucuronide	Braun et al., 1978
Rat	M	oral (corn oil)	10	45 (plasma)	4-6	17 - α 40 - β (total body)	80% in urine, 19% in feces	Kinetic data on elimination of urinary metabolites not provided.	Braun et al., 1977
Rat	F	oral (corn oil)	10	45 (plasma)	4-6	13 - α 33 - β (total body)	78% in urine, 19% in feces	Same as above	Braun et al., 1977
Rat	M	oral (corn oil)	100	NR	NR	13 - α 121 - β (total body)	72% in urine, 24% in feces	Pooled urine of males and females: 75% as PCP; 9% as PCP-glucuronide; 16% as TCH. Half-lives were 24 hours for PCP, 25 hours for PCP-glucuronide, and 32 hours for TCH.	Braun et al., 1977
Rat	F	oral (corn oil)	100	NR	NR	27 (total body)	54% in urine 43% in feces	Same as above	Braun et al., 1977
Monkey	M	oral (corn oil)	10	10-30	12-24	72 (plasma)	Urine half-life 41 hours	In urine as unchanged PCP; no metabolites.	Braun and Sauerhoff, 1976
	F	oral (corn oil)	10	10-30	12-24	84 (plasma)	Urine half-life 92 hours; 360 hours after single dose: 70% in urine; 18% in feces; 11% remained in tissues.	Same as above	Braun and Sauerhoff, 1976
Mouse	F	i.p. or s.c. (olive oil)	15-37	NR	NR	NR	72-83% excreted in urine in 4 days; about half in 24 hours; 5-7% in feces.	~45% as unchanged PCP; 14% as PCP conjugate; 40% as TCH.	Jakobson and Yllner, 1971

TABLE III-1 (cont.)

Species	Sex	Route (vehicle)	Dose (mg/kg)	Peak Blood Level (ppm)	Time to Peak Level (hours)	Half-Life (hours)	Excretion	Comments	Reference
Rat	NR	i.p. (olive oil or propylene glycol)	25	NR	NR	NR	70% in urine in 24 hours	43% as unchanged PCP; 5% as TCH; 38% as TCH conjugate; 14% as PCP conjugate.	Ahlborg et al., 1974
Mouse	NR	i.p. (olive oil or propylene glycol)	25	NR	NR	NR	70% in urine in 24 hours	41% as unchanged PCP; 24% as TCH; 22% as TCH conjugate; 13% as PCP conjugate.	Ahlborg et al., 1974

*Source: Modified from U.S. EPA, 1980

THC = Tetrachlorohydroquinone; NR = Not reported

TABLE III-2

Uptake of Pentachlorophenol (PCP) or Sodium Pentachlorophenate (NaPCP) by Wistar Rats After a 1-Week Exposure in Food or Drinking Water[a]

	Number of Animals	Intake of PCP (μmols/kg/24 hours)	Body Weight After 1 Week[b]	Plasma Concentration of PCP[c] (μM)
Controls	4	0	128 ± 10	0
PCP in food (350 ppm)	4	190 ± 11	114 ± 9	30 ± 3
NaPCP in food (350 ppm)	5	200 ± 14	116 ± 10	36 ± 5
NaPCP in drinking water (1.4 mM) (~320 mg/ℓ)	4	162 ± 16	108 ± 9[d]	40 ± 8
Single dose of PCP (40 μmol/kg; i.p.) 60 minutes before harmol	4	(40)	128 ± 2	55 ± 4

[a]Source: Meerman et al., 1983

[b]The body weight of the animals at the start of the experiments was 94±1 g (mean ± S.E.M.; n = 17).

[c]Blood was taken from the rats at the end of the experiments, 4 hours after the administration of harmol. All values are expressed as means ± S.E.M.

[d]Significantly different from controls at $p<0.1$ (Wilcoxon's Test 21).

Absorption rate constants were not determined in rats. The average absorption half-time was 2.7 hours in monkeys.

Braun et al. (1978) compared the absorption of pentachlorophenol in man with the values previously determined for monkeys and rats. Four healthy male volunteers ingested a single dose of 0.1 mg pentachlorophenol/kg bw (vehicle not specified). The average half-time for absorption was found to be 1.3±0.4 hours.

Other Routes of Exposure. Casarett et al. (1969) investigated the absorption of pentachlorophenol by two groups of 11 workers at two wood-treating plants in Honolulu. Workers in these two plants had mean pentachlorophenol concentrations in the urine of 2.2 and 2.4 ppm/1000 milliosmoles based on monthly samples during a 1-year period. Corresponding values in a group of workers not involved in the commercial use of pentachlorophenol ranged from ~0.01-0.1 ppm/1000 milliosmoles. An examination of the wood-treating process suggested that the absorption of pentachlorophenol indicated by the elevated urinary concentrations could have been from inhalation or dermal routes or both. In an effort to determine the significance of inhalation exposure as a route of absorption, two subjects spent 45 minutes in an enclosed area during a process that resulted in mean ambient pentachlorophenol concentrations of 230 and 432 ng/ℓ for the two subjects, respectively. Based on measurements of respiratory rates during exposure, total recovered pentachlorophenol in the urine, and estimates of tidal volume, these investigators concluded that the two workers absorbed 88 and 76% of the total potential inhalation dose.

Distribution

A number of investigators have examined the tissue distribution of pentachlorophenol and its metabolites. Jakobson and Yllner (1971) administered 15 or 37 mg [^{14}C]pentachlorophenol/kg bw to female NMRI mice (20-30 g) by single subcutaneous (s.c.) or intraperitoneal (i.p.) injection. The dosing vehicle was olive oil. The highest concentrations of ^{14}C activity after i.p. treatment were found in the gall bladder, the wall of the stomach fundus, the contents of the gastrointestinal tract, and the liver. Lesser concentrations were detected in the kidneys, heart and brain. Only traces of ^{14}C were found in the lungs. Concentrations in other organs were not measured. A similar distribution of ^{14}C activity was found after s.c. treatment. Radioactivity was measured by liquid scintillation spectrometry after oxidation of tissues from mice treated intraperitoneally and by whole body autoradiography in mice treated subcutaneously.

Braun et al. (1977) found the highest levels of radioactivity in the liver and kidneys of Sprague-Dawley rats given a single oral dose of 10 mg [^{14}C]pentachlorophenol in corn oil/kg bw. The lowest tissue concentrations were detected in the brain and fat. Radioactivity was measured in different tissues and blood plasma taken from one male and one female at 4, 24, 48, 72 and 120 hours post-treatment. The distribution was qualitatively similar in both males and females; however, plasma concentrations during the elimination phase were higher in females than in males. In this study, the authors noted that tissue/plasma ratios and renal clearance rates were much lower than would be predicted, based on the octanol/water partition coefficient and glomerular filtration rate. This observation was explained by the affinity of plasma proteins for pentachlorophenol (molar binding affinity

constant = 10^6). In this study, ~99% of the plasma pentachlorophenol was bound to plasma proteins. In another experiment, Braun et al. (1977) recovered 0.315% and 0.045% of an oral dose of 10 mg [^{14}C]pentachlorophenol/kg from liver and kidney, respectively, removed from male and female Sprague-Dawley rats at 9 days following treatment. Larsen et al. (1977) reported a similar distribution pattern in tissues removed from male and female rats 40 hours after gavage treatment with 31-40 mg/kg of ^{14}C-pentachlorophenol in corn oil.

Grimm et al. (1981) analyzed tissues and body fluids removed at autopsy from 21 human subjects in Northern Bavaria. The causes of death were not related to pentachlorophenol exposure. The median urine level was 0.0044 µg pentachlorophenol/mℓ, with median blood levels of 0.023 µg/mℓ. The highest concentrations of pentachlorophenol residues were found in the liver (0.067 µg/g), kidney (0.043 µg/g), brain (0.047 µg/g), spleen (0.019 µg/g) and body fat (0.013 µg/g).

Bioaccumulation and Retention

Using a pharmacokinetic model, Braun and Sauerhoff (1976) have estimated the accumulation of pentachlorophenol in rhesus monkeys during repeated dosing (Table III-3). This estimate was based on pharmacokinetic coefficients obtained from a single-dose oral study in which groups of 3 males and 3 females were given 10 mg/kg bw. Corn oil was the dosing vehicle. They predicted that 99% of the steady-state plasma concentration (50 µg/g) would be reached in 20 days. This steady-state concentration is ~2-5 times the peak plasma levels observed following a single oral dose.

TABLE III-3

Theoretical Time (days) to Reach 30, 70, 90, 97 and 99% of the Steady-State Plasma Concentration of Pentachlorophenol Following Consecutive Daily Doses of 10 mg/kg Pentachlorophenol to Monkeys*

Dose	Percentage of Steady-State	Number of Days that Dose was Given	Approximate Plasma Concentration of PCP (µg/g)
10 mg/kg	30	2	15
	70	6	35
	90	10	45
	97	15	49
	99	20	50

*Source: Braun and Sauerhoff, 1976

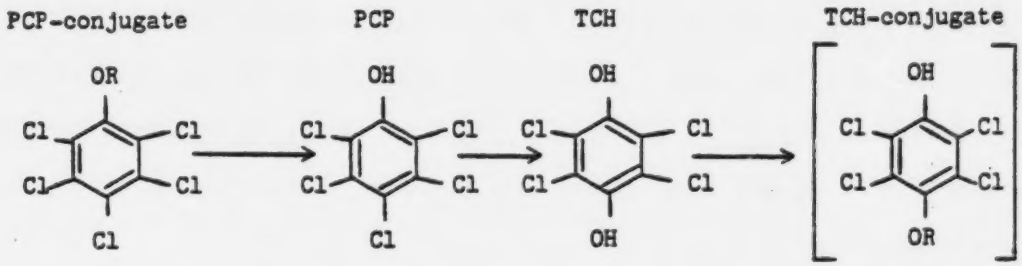
Using the same approach, Braun et al. (1978) also have estimated the accumulation of pentachlorophenol in humans during repeated exposure. This estimate was based on a single-dose oral study in which four male volunteers ingested 0.1 mg pentachlorophenol/kg bw. A one-compartment open-system model with first-order absorption, enterohepatic circulation, and first-order elimination was used. Under these conditions, 99% of steady-state levels would be reached in 8.4 days. Predicted steady-state plasma concentrations (~0.5 μg/mℓ) were approximately twice those observed following a single dose.

Other studies, summarized in the Excretion Section, also indicate that the excretion kinetics of pentachlorophenol are appreciably altered by repeated exposure compared with single exposure. Consequently, it is difficult to develop models which describe chronic accumulation of pentachlorophenol based on pharmacokinetic coefficients obtained from acute studies.

Metabolism

Several investigators have studied the metabolism of pentachlorophenol in rats and mice. Jakobson and Yllner (1971) administered 15-37 mg [^{14}C]pentachlorophenol/kg bw to female NMRI mice by s.c. or i.p. injection. Less than 0.05% of the administered radioactivity was converted to $^{14}CO_2$ or other volatile metabolites. The urinary metabolites were identified by paper chromatography and isotope dilution techniques. Of the total urinary radioactivity, ~45% was found to be unmetabolized pentachlorophenol and the remainder to be conjugated compounds. When the urine was treated with 3N hydrochloric acid at 100°C for 1 hour before analysis in order to hydrolyze the conjugates, two labeled compounds were detected.

Pentachlorophenol (PCP) constituted ~60% of the total radioactivity. Tetrachlorohydroquinone (TCH) accounted for the remainder of the urinary radioactivity. Based on these data, Jakobson and Yllner (1971) proposed the following metabolic pathway:



Similar results were obtained by Ahlborg et al. (1974) who determined the urinary metabolites of pentachlorophenol in NMRI mice and Sprague-Dawley rats when 10 or 25 mg [^{14}C]pentachlorophenol/kg bw was administered by i.p. injection or by gavage. Pentachlorophenol was dissolved in olive oil or propylene glycol. Total urinary radioactivity found to be unmetabolized pentachlorophenol was 41% for mice and 43% for rats. The major metabolite was identified as tetrachlorohydroquinone, accounting for 5% of the total urinary radioactivity in rats and 24% in mice. When the urinary conjugates were hydrolyzed by boiling with hydrochloric acid, all of the excreted radioactivity was present as pentachlorophenol (54% for mice and 57% for rats) and tetrachlorohydroquinone (43% for rats and 46% for mice). The mixed conjugates of pentachlorophenol and tetrachlorohydroquinone could not be identified as glucuronides, since the investigators found that tetrachlorohydroquinone was found to be a potent inhibitor of β-glucuronidase.

Braun et al. (1977) obtained similar results in Sprague-Dawley rats. Within 24 hours, 48% of the administered dose (10 mg/kg by gavage) had been excreted in the urine as pentachlorophenol, 10% as tetrachlorohydroquinone, and 6% as conjugates. The isolated conjugate, but not the complete urine, could be hydrolyzed by ß-glucuronidase. Enzymatic hydrolysis of the isolated conjugate resulted in one product, which was subsequently identified as pentachlorophenol by mass spectrometry and co-chromatographic thin-layer chromatography.

Leighty and Fentiman (1982) have speculated that the in vivo retention of pentachlorophenol by lipid-containing tissues involves conjugation with fatty acids. They demonstrated the conjugation of pentachlorophenol with palmitic acid in an in vitro rat liver coenzyme A fortified microsomal system, but this conjugate has not been found in vivo.

Little is known of the metabolism of pentachlorophenol in humans. Ahlborg et al. (1974) analyzed the urine from two occupationally exposed spraymen 24 hours following exposure. The urine was hydrolyzed with concentrated hydrochloric acid, extracted with diethyl ether, methylated with diazomethane and analyzed by GC/MS. Both pentachlorophenol and tetrachlorohydroquinone were found (proportions not specified), indicating that metabolism of pentachlorophenol in humans is similar to that in rats and mice. This study provided no information on the existence of possible conjugated metabolites in human urine.

Excretion

Rodents. Jakobson and Yllner (1971) administered 15 or 37 mg [^{14}C]-pentachlorophenol/kg bw to female NMRI mice by s.c. or i.p. injection. Excretion was rapid, with approximately half of the total dose excreted during the first 24 hours. Most of the excreted radioactivity (94%) was detected in the urine, ~6% was in the feces, and <0.05% was detected in the expired air. By 30 days postinjection, <1% of the dose remained in the mice.

Larsen et al. (1972) reported an analysis of the excretion kinetics of [^{14}C]pentachlorophenol in female rats (strain not specified) following a single oral dose (37-41 mg/kg bw). The urine was the major route of excretion, with 65.2% of the administered radioactivity recovered in the urine within 72 hours. Less than 0.04% of the administered radioactivity was detected in expired air. Urinary excretion was found to be biphasic, with half-lives of 10 hours and 102 days. The accuracy of these half-lives has been questioned on several points by Braun et al. (1977) who stated that unless total recovery of the dose, which was not reported by Larsen et al. (1972), is known to approach 100%, use of the sigma-minus plot by Larsen et al. (1972) might have caused gross errors in the estimation of elimination rates. Braun et al. (1977) noted that Larsen et al. (1972) did not consider fecal excretion in their calculations. For the purpose of their analysis, Larsen et al. (1972) assumed that fecal elimination was constant. Their analysis of pooled fecal samples collected throughout the 10-day collection period indicated elimination of 9.2-13.2% of the dose by this route.

Biphasic elimination has also been reported by Braun et al. (1977). Single oral doses of 10 or 100 mg [^{14}C]pentachlorophenol/kg bw were administered to groups of 3 male and 3 female Sprague-Dawley rats. The urine was the major route of elimination, accounting for 80.11 and 78.13% of the dose in males and females, respectively, following administration of 10 mg/kg bw and 72.1% (males) and 54.4% (females) following a 100 mg/kg bw dose. The feces also contained high levels of radioactivity, accounting for 18.8% (males) and 19.3% (females) as well as 24.5% (males) and 42.8% (females) of the administered radioactivity following doses of 10 and 100 mg/kg bw, respectively. Expired air contained only 0.2% of the administered radioactivity following a dose of 10 mg/kg bw. Excretion in the expired air was not measured following the 100 mg/kg bw dose.

Biphasic elimination kinetics were observed in the male rats receiving either 10 or 100 mg [^{14}C]pentachlorophenol/kg bw and in females receiving 10 mg/kg bw. Elimination coefficients were calculated by a nonlinear parameter estimation program. The half-lives of the rapid phase of elimination were 17 and 13 hours for the male rats dosed with 10 and 100 mg/kg bw, respectively, and 13 hours for the female rats receiving 10 mg/kg bw. The corresponding half-lives for the slower phase of elimination were 40, 121 and 33 hours, respectively. More than 90% of the administered dose was eliminated during the rapid phase of excretion. Excretion in females receiving 100 mg/kg bw was monophasic with a half-life of 27 hours. The investigators offered no reason for the apparent first-order elimination process in the high dose females; however, as described above, fecal and urinary elimination of ^{14}C was different in comparison with the other treatment groups.

Two factors appeared to contribute to the slow phase of elimination. The retention of radioactivity in the liver was considered to be the major contributor to the slow phase of elimination. At the latter time points, the liver contained ~70% of the total body burden of pentachlorophenol derived radioactivity. Also, as the plasma levels decreased, binding to the limited number of high-affinity sites on plasma proteins became a greater factor, reducing the renal clearance of pentachlorophenol.

Biphasic elimination was also observed in Wistar rats by Meerman et al. (1983), but the rates were greater than those observed in Sprague-Dawley rats. Sodium pentachlorophenate was administered intravenously, in contrast to oral dosing used in the studies with Sprague-Dawley rats, at a single dose of 40 μmol/kg (~10.6 mg/kg) as pentachlorophenol. The initial rapid phase of elimination had a half-life of 2.14 hours. The half-life of the slow phase of elimination was 7.24 hours.

Subhuman Primates. Braun and Sauerhoff (1976) administered a single oral dose of 10 mg [^{14}C]pentachlorophenol/kg bw to groups of 3 male and 3 female rhesus monkeys. Excretion was monophasic, with half-lives of 40.8 hours for males and 92.4 hours for females. As in rodents, the urine was the major route of excretion, accounting for 72-78% of the dose in males and 69-72% of the dose in females. Approximately 12% of the dose was excreted in the feces of males and 13-24% in females. The investigators suggested that the long biological half-lives observed were the result of extensive biliary excretion and enterohepatic recirculation.

The role of biliary excretion was further investigated by Ballhorn et al. (1981) and Rozman et al. (1982). Ballhorn et al. (1981) administered 30 or 50 mg [^{14}C]pentachlorophenol/kg bw to groups of two male rhesus monkeys each. After 24 hours, one monkey from each group was transfered to a diet containing 4% cholestyramine. This treatment increased fecal elimination by 9- to 14-fold and decreased urinary elimination by 2- to 6-fold. The authors concluded that cholestyramine interrupts the enterohepatic circulation of pentachlorophenol and its metabolites.

Rozman et al. (1982) repeated the studies of Ballhorn et al. (1981), using male rhesus monkeys provided with a bile duct by-pass. Each monkey functioned as its own control, with the control and cholestyramine treatment periods separated by 4 weeks. Excretion was measured for 6 days after each dose. During the first 24 hours after dosing, excretion in the urine, feces and bile accounted for 20, 0.5 and 20% of the administered pentachlorophenol, respectively. Addition of 4% cholestyramine to the diet reduced urinary excretion during days 2-6 from 35 to 5% of the administered dose and increased fecal excretion from 3-54%. Total biliary excretion decreased from 70 to 52% of the dose. The authors concluded that cholestyramine both interrupts enterohepatic recycling and increases the direct absorption of pentachlorophenol across the intestinal wall.

Human. Bråun et al. (1978) orally administered 0.1 mg pentachlorophenol/kg bw to four male volunteers. They reported a plasma half-life of 30.2 hours. Within 168 hours, 74% of the administered dose had been eliminated in the urine as pentachlorophenol and 12% as pentachlorophenol-glucuronide. An additional 4% was excreted in the feces as pentachlorophenol and pentachlorophenol-glucuronide combined.

Bevenue et al. (1967a) measured the urinary levels of pentachlorophenol in 541 people (predominately male) in Honolulu and adjacent areas, 247 of which had some occupational exposure to the compound. Their data implied biphasic excretion kinetics. Urinary concentrations decreased 34.7%/day over the first 1-2 days following exposure, compared with 3.3%/day for 10-23 days following exposure and 0.85%/day for 64-115 days following exposure.

Casarett et al. (1969) used epidemiological methods to investigate the excretion of pentachlorophenol by workers in a wood-treating plant in Honolulu. The data indicated a possible difference in excretion kinetics between single high-level and chronic low-level exposures. Precise values were not reported. Following a single inhalation exposure, urinary excretion half-lives of ~10 hours were observed in two individuals; however, following chronic exposure, urine concentrations decreased only 60-80% when the workers were absent from work for up to 18 days. The authors postulated that this apparent difference in excretion kinetics between acute and chronic exposures may be attributable to a "... four compartment system for chronic inhalation exposure consisting of lung, plasma proteins, urine and tissue depots."

Begley et al. (1977) determined pentachlorophenol concentrations in the blood and urine of 18 workers at a Honolulu wood-treating plant on the last day of work before a 20-day vacation, on days 3, 6, 13 and 20 of vacation, and on day 51 after they returned to work. Over the 20-day vacation period, blood and urine levels fell to <50% of the prevacation values. Interestingly, there was a slight rise in blood levels between days 3 and 6 of the vacation, possibly indicating mobilization of tissue depots. These data

imply a urinary elimination half-time of 19-20 days for occupational exposure to pentachlorophenol.

Summary

The available data indicate that the biological handling of pentachlorophenol is similar across mammalian species. Pentachlorophenol is rapidly absorbed following oral, dermal or inhalation exposure. Once absorbed, pentachlorophenol is distributed throughout the body, accumulating in the liver, kidneys, brain, spleen and fat (Braun et al., 1977; Grimm et al., 1981; Jakobson and Yllner, 1971). The pentachlorophenol in the plasma is highly protein-bound, which greatly reduces the tissue/plasma concentration ratios and the renal clearance rate (Braun et al., 1977).

Pentachlorophenol apparently is not readily metabolized, since a large portion of the administered dose is excreted unchanged by all species tested. The major metabolic reactions of pentachlorophenol are conjugation to form the glucuronide and an oxidative dechlorination to form tetrachlorohydroquinone.

Based on a single dose study, Braun et al. (1978) predicted that steady-state levels would be reached in man within 8-9 days during chronic exposure. Under these conditions, maximum blood levels would be only about twice those observed following a single dose. Other investigators (Casarett et al., 1969; Begley et al., 1977) have reported half-lives for elimination of ~10 hours following an acute exposure, which is consistent with the value obtained by Braun et al. (1978); however, after chronic exposure, half-lives of ~20 days were reported. Pentachlorophenol may, therefore, have a greater potential for accumulation than the acute studies would indicate.

The major route of elimination is in the urine. The feces represents a minor route of excretion. Only trace amounts of metabolites have been detected in expired air. Biliary excretion occurs; however, extensive enterohepatic recirculation prevents this from being a major factor in the elimination of pentachlorophenol. Elimination is generally biphasic, with an initial rapid phase, followed by a period of much less rapid elimination. This pattern has been observed in rats (Braun et al., 1977) and man (Bevenue et al., 1967a), but not in subhuman primates (Braun and Sauerhoff, 1976).

IV. HUMAN EXPOSURE

Humans may be exposed to chemicals such as pentachlorophenol (PCP) from a variety of sources, including drinking water, food, ambient air, occupational settings and consumer products. This analysis of human exposure to PCP is limited to drinking water, food and ambient air because those media are considered to be sources common to all individuals. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and on several factors over which there is little control. Where one lives, works and travels, what one eats, and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Detailed information concerning the occurrence of and exposure to PCP in the environment is presented in another document entitled "Occurrence of Pesticides in Drinking Water, Food and Air" (Johnston et al., 1984). This chapter summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food and air.

In the Exposure Estimation section of this chapter, available information is presented on the range of human exposure and intake for PCP from drinking water, food and ambient air for the 70 kg adult male. It is not possible to provide an estimate of the number of individuals experiencing specific combined exposures from those three sources. However, the Summary

section of this chapter provides some insight into the range of intake values suggested by the available data.

Exposure Estimation

Drinking Water. Levels of PCP in drinking water vary from one location to another. The highest level of PCP reported in the available surveys was 12 µg/ℓ in samples of finished drinking water from a city in Michigan (Boland, 1981). However, levels of PCP in drinking water typically appear to be somewhat lower. Analysis of unpublished data from the EPA Drinking Water Program suggested that median levels of PCP in drinking water systems would be 0.051 µg/ℓ (Cirelli, 1978); levels may be as low as 0.0 µg/ℓ. The available monitoring data are not sufficient to determine regional variations in exposure levels for PCP.

The daily intake of PCP from drinking water was estimated using the assumptions presented in Table IV-1 and the values presented above. The estimates in Table IV-1 indicate that daily PCP intake from drinking water ranges from 0.0-0.34 µg/kg/day. However, the values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

Diet. Data are limited on the dietary intake of PCP in the United States. Daily intake of PCP for adults and for infants and toddlers by food group was estimated by FDA for fiscal year 1979 (FDA, 1982a,b) (Table IV-2). The estimates of daily intake of PCP from food are based on analyses of composite food samples obtained in market basket surveys. Intake calculated on the basis of weight (µg/kg/day) is greatest for the adult male and

TABLE IV-1

Estimated Drinking Water Intake of Pentachlorophenol*

Drinking Water Concentration (µg/ℓ)	Intake (µg/kg/day)
0.0	0.0
0.051	0.0015
12.0	0.34

*Assumptions: 70 kg adult male consuming 2 ℓ of water/day

TABLE IV-2

Estimated Daily Intake of Pentachlorophenol by Food Class for Adult Male, 6-Month-Old Infant and 2-Year-Old Toddler[a]

Food Group[b]	Intake (µg/kg/day)[c]
Adult male	
II. Meat, fish and poultry	0.005
X. Oils and fats	0.001
Total	0.006
Infant	
IX. Oils and fats	0.0045
Toddler	
IX. Oils and fats	0.0018

[a]Source: FDA, 1982a,b

[b]Includes only those groups that contained quantifiable levels of PCP.

[c]Values were obtained by dividing intake in µg/day by 69.1 kg for the adult male, 8.2 kg for infants, and 13.7 kg for toddlers.

lowest for the toddler. For the adult male, the highest intakes of PCP result from consumption of the meat, fish and poultry group and the oils and fats group. Oils and fats are also a source of intake of PCP for the infant and toddler.

Additional data were obtained on the estimated total dietary intake of PCP for adults in 1974-1979 and for infants and toddlers in 1975-1979 (FDA, 1980a,b, 1982a,b) (Table IV-3). The average total intakes for adults, infants and toddlers over the years studied were 0.010, 0.005 and 0.009 µg/kg/day, respectively.

Using the above data, the daily intake of PCP is estimated to be 0.010 µg/kg/day. This value does not account for variances in individual exposure.

Dietary levels of PCP may vary somewhat with geographic location (Table IV-4). The highest levels in the FY 79 studies occurred in the Northeast, where the estimated PCP intakes for adult males, infants and toddlers were 0.011, 0.001 and 0.006, respectively.

Air. No data were obtained on levels of PCP in ambient air. Therefore, the intake of PCP from ambient air could not be estimated.

Summary

Data on the intake of PCP from drinking water, food and ambient air are insufficient for use in determining which of the three sources is the major contributor to total intake. In addition, an acceptable daily intake (ADI)

TABLE IV-3

Estimated Total Daily Intake of Pentachlorophenol for Adult Male, Infant and Toddler[a]

Year	Intake (µg/kg/day)		
	Adult Male	Infant (6 months)	Toddler (2 years)
1974	0.0109	--	--
1975	0.0240	0.0154	0.0214
1976	0.0174	Trace[b]	0.0162
1977	0.0009	ND	0.0060
1978	ND	ND	ND
1979	0.0060	0.0045	0.0018
Average	0.010	0.005	0.009

[a]Source: FDA, 1980a,b, 1982a,b

[b]Trace residues were not included in calculating the average.

ND = Not detected

TABLE IV-4

Estimated Daily Intake of Pentachlorophenol
for Adults, Infants and Toddlers by Geographic Region

Region	Intake (μg/kg/day)		
	Adult Male	Infant (6 months)	Toddler (2 years)
Northeast	0.011	0.001	0.006
North Central	0.005	--	--
South	--	--	--
West	0.008	--	--

Source: FDA, 1982a,b

for PCP has not been established by FDA (1981). However, EPA (1980) has established an ADI of 2.1 mg/day based on chronic toxicity data obtained from Schwetz et al. (1978) and Koliba et al. (1978). In addition, an estimated intake of PCP from food and drinking water may be determined based on the data presented in the Drinking Water and Diet Sections. Assuming an average intake of 0.010 µg/kg/day of PCP from food, the estimated total daily intake of PCP from food and water ranges from 0.010-0.35 µg/kg/day.

References

Boland, P.A. 1981. National screening program for organics in drinking water. Part II. Data. Prepared by SRI International, Menlo Park, CA, for Office of Drinking Water, U.S. EPA, Washington, DC. EPA Contract No. 68-01-4666.

Cirelli, D.P. 1978. Pentachlorophenol: Position document 1. Special Pesticide Review Division, U.S. EPA, Washington, DC. EPA/SPRD-80/85.

FDA (Food and Drug Administration). 1980a. Compliance program report of findings. FY 77 total diet studies -- Adult (7320.73). Food and Drug Administration, U.S. DHEW, Washington, DC.

FDA (Food and Drug Administration). 1980b. Compliance program report of findings. FY 77 total diet studies -- Infants and toddlers (7320.74). Food and Drug Administration, U.S. DHEW, Washington, DC.

FDA (Food and Drug Administration). 1981. The FDA surveillance index. Bureau of Foods, Food and Drug Administration, Washington, DC.

FDA (Food and Drug Administration). 1982a. Compliance program report of findings. FY 79 total diet studies -- Adult (7305.002). Food and Drug Administration, U.S. DHHS, Washington, DC. FDA/BF-82/98.

FDA (Food and Drug Administration). 1982b. Compliance program report of findings. FY 79 total diet studies -- Infants and toddlers (7305.002). Food and Drug Administration, U.S. DHHS, Washington, DC. FDA/BF-82/97.

Johnston, P., F. Letkiewicz, D. Borum, et al. 1984. Occurrence of pesticides in drinking water, food and air. Interim draft report. Prepared by JRB Associates, McLean, VA, for Office of Drinking Water, U.S. EPA, Washington, DC.

Koliba et al. 1978.

Schwetz et al. 1978.

U.S. EPA. 1980. Water Quality Criteria Documents. Federal Register. 45: 79318-79379.

V. HEALTH EFFECTS ON ANIMALS

General Toxicity

Acute Toxicity. The acute toxicity of pentachlorophenol and sodium pentachlorophenate, as the LD_{50} or LD_{Lo}, are summarized in Table V-1. Following oral, i.p. or percutaneous administration, animals exhibit a rise in body temperature and respiration rate (McGavack et al., 1941; Deichmann et al., 1942; Farquharson et al., 1958). As coma develops, respiration becomes slower and dyspneic, with cardiac and muscular collapse and terminal asphyxial convulsive movements occurring near death. The onset of rigor mortis is immediate and pronounced. Other signs observed with varying frequency in pentachlorophenol poisoning include increased blood pressure, hyperglycemia and glycosuria, hyperperistalis and decreased urinary output. Most of the older studies and many of the more recent studies of acute toxicity used technical grade pentachlorophenol containing varying concentrations of chlorinated dibenzo-p-dioxins and dibenzofurans. In these studies, it is often impossible to differentiate the effects caused by pentachlorophenol from those caused by the contaminants.

Most of the information on the acute health effects of pentachlorophenol is based on two older studies by McGavack et al. (1941) and Deichmann et al. (1942). The chemical purity of the pentachlorophenol used by these investigators was not specified; thus, the degree to which chlorinated dioxins and dibenzofurans contributed to the observed results is unknown.

Deichmann et al. (1942) reported extensive vascular damage and heart failure in rats, rabbits, guinea pigs and dogs following a single oral administration of pentachlorophenol. Degenerative changes in the motor

TABLE V-1

Acute Toxicity of Pentachlorophenol and Sodium Pentachlorophenate[a]

Compound	Route	Species	Dose Administered (mg/kg)	Response[b]	Reference
Pentachlorophenol	oral (fuel oil)	rats	27 (0.5% solution)	LD_{50}	Deichmann et al., 1942
	oral (olive oil)	rats	78 (1% solution)	LD_{50}	Deichmann et al., 1942
	oral	rats	30	LD_{50}	Deichmann, 1943
	oral	rats (male)	205	LD_{50}	Dow Chemical Co., 1969a
	oral	rats (female)	135	LD_{50}	Dow Chemical Co., 1969a
	oral	rats	50-140	LD_{50}	Meister, 1972
	oral	mice	74	LD_{50}	Ahlborg and Larsson, 1978
	oral	hamsters	168	LD_{50}	Cabral et al., 1979
	oral	rabbits	70	LD_{Lo}	Deichmann et al., 1942
	i.p.	rats	56	LD_{50}	Farquharson et al., 1958
	i.p.	rabbits	135	LD_{Lo}	Dittmer, 1959
	s.c.	rats	100	LD_{50}	Deichmann, 1943
	s.c.	mice	46	LD_{Lo}	BRL, 1968a
	s.c.	rabbits	70	LD_{Lo}	Deichmann et al., 1942

TABLE V-1 (cont.)

Compound	Route	Species	Dose Administered (mg/kg)	Response[b]	Reference
	s.c.	dogs	135	LD_{Lo}	Dittmer, 1959
	dermal	rats	105	LD_{50}	Noakes and Sanderson, 1969
	dermal	rabbits	40	LD_{Lo}	Deichmann et al., 1942
Sodium Pentachlorophenate	oral	rats	210.6	LD_{50}	Deichmann et al., 1942
	oral	rats	210	LD_{50}	Dow Chemical Co., 1969b
	oral	rabbits	275	LD_{50}	Dow Chemical Co., 1969b
	oral (aqueous)	rabbits	250-300 (5% solution)	LD_{Lo}	Deichmann et al., 1942
	oral	rabbits	550	LD_{Lo}	McGavack et al., 1941
	oral	guinea pigs	80-160	LD_{50}	Dow Chemical Co., 1969b
	i.p.	rats	30	LD_{50}	Hoben et al., 1976
	i.p.	rabbits	135	LD_{Lo}	McGavack et al., 1941
	s.c.	rats	80	LD_{50}	Deichmann et al., 1942
	s.c.	mice	56	LD_{Lo}	Dittmer, 1959
	s.c.	rabbits	100	LD_{Lo}	Deichmann et al., 1942
	s.c.	rabbits	275	LD_{Lo}	McGavack et al., 1941

TABLE V-1 (cont.)

Compound	Route	Species	Dose Administered (mg/kg)	Response[b]	Reference
	s.c.	dogs	135	LD_{Lo}	Dittmer, 1959
	i.v.	rabbits	22	LD_{Lo}	Deichmann et al., 1942
	inhalation	rats	11.7	LD_{50}	Hoben et al., 1976
	dermal	rabbits	250	LD_{Lo}	Deichmann et al., 1942
	dermal	rabbits	100-300 (20% solution)	LD_{50}	Dow Chemical Co., 1969b
	dermal	rabbits	512	LD_{Lo}	McGavack et al., 1941
	dermal	guinea pigs	266	LD_{Lo}	Dittmer, 1959

[a]Source: NIOSH, 1981

[b]LD_{50} = Dose lethal to 50% of recipients; LD_{Lo} = Lowest dose observed to cause lethality

neurons and slight capillary congestion of the brain and spinal cord have been reported in rabbits that received a single oral dose of sodium pentachlorophenate (McGavack et al., 1941).

McGavack et al. (1941) and Deichmann et al. (1942) administered single dermal applications of a 10% sodium pentachlorophenate solution (60-600 mg/kg) to rabbits. At all doses, microscopic changes including widespread foci of atrophy and necrosis, thinning and disappearance of the upper skin layers, and irregular thickening (hyperkeratinization and hypertrophy of the hair follicles) at the site of treatment were observed. The subcutaneous layer underwent a gradual fibrillar thickening with hyaline degeneration following an initial period in which this layer became either thick and edematous or thin and flattened. Grossly, dermal exposure resulted in pronounced edema and inflammation with subsequent wrinkling, cracking, desquamation and loss of hair.

The acute effects of pentachlorophenol were studied by Nishimura et al. (1982) and Madge (1981). Nishimura et al. (1982) administered by gavage single doses of 0, 10, 30, 60, 120 or 150 mg sodium pentachlorophenate in water (>90% pure)/kg bw to male Wistar rats. The animals were sacrificed after 24 hours of fasting. All doses >10 mg/kg resulted in a significant ($p<0.01$) increase in liver wet weight/unit bw. Absolute liver weight and body weight data were not given. There was a dose-related increase in hepatic glycogen and lactate levels, with glycogen concentrations reaching levels >10-fold the control values, at doses of 120-150 mg/kg. No histological examinations were conducted.

Madge (1981) investigated the effect of pure and technical grade pentachlorophenol on intestinal absorption in the mouse. A single oral dose of 5 mg/kg bw was administered and, 7 days later, the intestine was removed and solute accumulation and solvent transfer were measured in vitro. Nonpurified grade pentachlorophenol decreased the absorption of D-glucose, apparently by increasing the rate of D-glucose metabolism. Fluid transfer was unaffected by either treatment. Further details of the study were not available in the asbstract.

Chronic and Subchronic Toxicity. As with acute doses, much of our knowledge of the chronic and subchronic toxicity of pentachlorophenol is based on older studies using pentachlorophenol of undetermined purity.

Deichmann et al. (1942) investigated the effects of subchronic exposure in rats, cats and rabbits. No gross signs of toxicity were observed in groups of 10 rats fed diets containing 588 ppm (588 mg/kg diet) pentachlorophenol for 26 weeks (5 mg/rat/day) or 300 ppm (300 mg/kg diet) for 28 weeks (3.9 mg/rat/day). Microscopic examination revealed unspecified histological abnormalities, which were not further described. Rats in both dose groups showed decreases in food consumption and body weight gain attributed by the authors to the unpleasant taste of the compound. Because the study by Deichmann et al. (1942) does not provide food consumption and body weight data, estimates of mg/kg bw doses cannot be made.

Deichmann et al. (1942) also administered daily gavage doses of 35 mg pentachlorophenol/kg bw as a 0.5% solution of the sodium salt to five rabbits for 15 consecutive days. Over the next 19 days, the daily dose was

gradually raised to 600 mg/kg bw. Death occurred following ingestion of a total of 1.9-3.9 g/kg bw. Blood concentrations at death ranged from 14-39 mg% compared with 8 mg% following a single lethal dose (LD_{50} data), indicating that a tolerance may develop following repeated administration of sublethal oral doses. In parallel experiments, no signs of toxicity as determined by blood and tissue concentrations were observed in a group of 23 rabbits that received daily gavage doses of 3 mg/kg bw, 6 day/week for a total of 90 doses or in groups of 4 cats that received diets equivalent to 1.25 or 2.5 mg/kg bw/day for 10 weeks.

Deichmann et al. (1942) also investigated the effect of subchronic (100 days) dermal administration of 41 mg sodium pentachlorophenate/kg bw in fuel oil to six rabbits for 6 days/week. They reported mild irritation, but no wrinkling, cracking or hair loss. Body weight gain was normal and there were no fatalities.

In parallel studies, Deichmann et al. (1942) investigated the subchronic to chronic dermal toxicity of pentachlorophenol to rabbits. Doses of 1-50 mg/kg bw as a 4% solution in fuel oil were applied to the dorsal skin once or twice a week for 6-61 weeks. The local effects observed were similar to those seen following the application of a single large dose (Acute Toxicity Section). A 2-3°F increase in rectal temperature was observed within 8 hours of the beginning of treatment and regularly thereafter with the increase in dosage levels. Though no specific symptoms were reported, 8 of the 20 rabbits treated died during the study. A dose-related increase in a number of unspecified gross and histological tissue changes was reported among the surviving rabbits.

In a series of experiments, McGavack et al. (1941) administered a solution of sodium pentachlorophenate of unknown purity subcutaneously, once a day for up to 60 days to groups of six rabbits. The doses used were 1/20, 1/10 or 1/4 of the minimum lethal dose (276 mg/kg). In the two high-dose groups, death occurred by days 15 and 8, respectively. There were no deaths in the low-dose group; however, 3 of the 6 rabbits exhibited signs of acute poisoning. In a parallel experiment, daily i.p. doses of 15 mg/kg produced death in an average of 11 days. Toxic symptoms for both the s.c. and i.p. routes were similar to those observed following acute intoxication. Death was accompanied by convulsive seizures that were less intense than those observed in acutely poisoned rabbits. Blood analysis revealed secondary anemia, leukopenia with relative lymphocytosis, polycythemia and increased blood sugar levels. Autopsy findings included hemorrhages and congestion in the lungs and kidneys, hypertrophy of the pulmonary artery, cloudy swelling of the liver and degenerative changes in the kidney tubules. Numerous lesions were observed in the brain and spinal cord, including capillary congestion, slight chromatolysis of nerve cells, diffuse focal areas of perivascular lymphocytic and mononuclear infiltration, and circumscribed subpial collections of unspecified small round cells.

Using technical grade pentachlorophenol reportedly containing 200 ppm octachlorodibenzo-p-dioxin and 82 ppm "preoctachlorodibenzo-p-dioxin," Knudsen et al. (1974) fed groups of 10 male and 10 female Wistar rats diets containing 0, 25, 50 or 200 ppm (0, 25, 50 or 200 mg/kg diet) pentachlorophenol for 12 weeks. Food consumption and behavior were normal throughout the treatment period; however, growth depression was noted in the female rats receiving 200 mg/kg diets. Microsomal liver enzyme induction and

increased liver weight were observed at dietary levels of 50 and 200 mg/kg diet. A dose-related decrease in calcium deposits in the kidneys of females was also observed (8/10 in controls, 2/10 in high-dose group). In this study, the NOEL was 25 mg/kg diet.

Mild but unspecified liver and kidney damage were reported in rats treated with 100 mg sodium pentachlorophenate/kg bw by daily gavage for 20 days (Dow Chemical Co., 1969a).

More recently, three groups of investigators compared the effects of subchronic administration of pure and technical grades of pentachlorophenol (Table V-2). Technical grade pentachlorophenol produced a number of effects that were not observed with the pure compound. These effects are consistent with contamination of the technical product by biologically active chlorinated dibenzo-p-dioxins and dibenzofurans.

Johnson et al. (1973) tested pure and technical grade pentachlorophenol in the chick edema bioassay, rabbit ear bioassay and a 90-day rat feeding study. The technical grade, but not the pure compound, produced positive results in both the chick edema assay and the rabbit ear assay (ie., chloracne). In the 90-day feeding study, Sprague-Dawley rats (number not specified) were fed diets resulting in a dose of 3, 10 or 30 mg/kg bw/day. Hematological changes included depression of erythrocytes, hemoglobin and packed cell values, and pathological changes consisting of focal hepatocellular degeneration and necrosis were reported with a dose of 30 mg technical grade pentachlorophenol/kg bw, while changes in clinical chemistry as well as increased liver weight and kidney weight were observed at all doses.

TABLE V-2

Subchronic Effects of Technical and Pure Pentachlorophenol on Rats*

Pentachlorophenol	Impurities	Dose and Duration of Study	Effects	Reference
Technical grade	1980 ppm octachlorodibenzo-p-dioxin 19 ppm hexachlorodibenzo-p-dioxin	3, 10 and 30 mg/kg/day in the feed for 90 days	Elevated serum alkaline phosphatase. Decreased serum albumin, hemoglobin and packed cell volume. Increased liver and kidney weights, with minimal focal hepatocellular degeneration and necrosis.	Johnson et al., 1973
Pure grade	No detectable chlorinated dioxins	3, 10 and 30 mg/kg/day x 90 days	Increased liver and kidney weights. but no gross or microscopic tissue changes.	Johnson et al., 1973
Improved technical	30 ppm octachlorodibenzo-p-dioxin 1.0 ppm hexachlorodibenzo-p-dioxin	3, 10 and 30 mg/kg/day x 90 days	Results similar to those obtained with pure pentachlorophenol.	Johnson et al., 1973
Technical grade	1380 ppm octachlorodibenzo-p-dioxin 520 ppm heptachlorodibenzo-p-dioxin 8 ppm hexachlorodibenzo-p-dioxin 260 ppm octachlorodibenzofuran 400 ppm heptachlorodibenzofuran 0 ppm hexachlorodibenzofuran 40 ppm pentachlorodibenzofuran 4 ppm tetrachlorodibenzofuran	20, 100 and 500 ppm in the diet x 8 months	Hepatic porphyria and increased hepatic aryl hydrocarbon hydroxylase and glucuronyl transferase activities, liver weight, cytochrome P-450 and microsomal heme. Decreased body weight at 500 ppm.	Goldstein et al., 1977
Pure grade	<0.1 ppm of all the above contaminants	20, 100 and 500 ppm in the diet x 8 months	No significant effect on the above parameters except glucuronyl transferase, which was increased at 500 ppm. Decreased body weight gain at 500 ppm which was comparable to that observed for the technical grade pentachlorophenol.	Goldstein et al., 1977
Technical grade	86% Purity. Analysis of impurities not reported.	50 or 500 mg/kg diet for 10-12 weeks	Increased incidence of methylcholanthrene-induced transplaned tumors. Increased mortality following primary Moloney sarcoma virus (MSV) inoculation and secondary challenge with MSV-transformed sarcoma cells (MSB). Depression of T-cell cytolytic activity. Enhanced macrophage phagocytosis.	Kerkvliet et al., 1982a,b
Pure grade	99+% Purity	50 or 500 mg/kg diet for 10-12 weeks	Enhanced splenic tumor development following MSV/MSB challenge.	Kerkvliet et al., 1982a,b

*Source: NIOSH, 1981

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When pure pentachlorophenol was used, the only changes observed were changes in kidney weight at the high dose and changes in liver weight at the two higher doses. In this study, 3 mg/kg/day represents a no effect level for pure pentachlorophenol based on increases in liver weights. Johnson et al. (1973) also tested an "improved" grade of pentachlorophenol, described in Table V-2 which produced results similar to those obtained with purified pentachlorophenol.

Goldstein et al. (1977) fed female Sherman rats (6/group) diets containing 0, 20, 100 or 500 ppm (0, 20, 100 or 500 mg/kg diet) pure or technical grade pentachlorophenol for 8 months, at which time survivors were sacrificed. The only reported effects of the pure compound was an increase in glucuronyl transferase and hepatic aryl hydrocarbon hydroxylase activities and decreased body weight at a dose of 500 mg/kg diet. In contrast, technical grade pentachlorophenol produced porphyria and increases in liver cytochrome P-450 at doses of 100 and 500 mg/kg diet and glucuronyl transferase induction. Also increased hepatic aryl hydrocarbon hydroxylase activity was observed at doses as low as 20 mg/kg diet.

Kerkvliet et al. (1982a,b) compared the immunotoxic effects of the pure and technical grades of pentachlorophenol. Male C57Bl/6 (B6) mice were maintained on diets containing 50 or 500 ppm (50 or 500 mg/kg diet) for 10-12 weeks before immune testing. The immune system was assessed by low-dose syngenic tumor transplant, Moloney sarcoma virus-induced tumor susceptibility, resistance to encephalomyocarditis virus infection, and allogenic sensitization for T-cell and macrophage activation.

No gross indications of toxicity were observed during the treatment period. Histological examinations revealed pathological changes only in the liver, with similar lesions resulting from exposure to both pure and technical grades of pentachlorophenol. There was a dose-related swelling of hepatocytes accompanied by nuclear swelling and vacuolization with eosinophilic inclusion bodies. Mild to moderate multifocal necrosis was observed in the high dose group. Technical grade pentachlorophenol produced a dose-dependent delay and suppression of peak splenic antibody production and serum antibody titers. No decrease in humoral antibody response was observed in rats receiving purified pentachlorophenol. Pure pentachlorophenol did enhance the development of splenic tumors in mice challenged with Moloney sarcoma virus-induced tumor cells. The incidences of splenic tumor development following MSV/MSB challenges were 0, 22 and 44% in mice receiving 0, 50 and 500 mg pure pentachlorophenol/kg diet, respectively.

Additional studies of the effects of pentachlorophenol were performed by Schwetz et al. (1978) and Greichus et al. (1979). Schwetz et al. (1978) fed diets resulting in a dose of 0, 1, 3, 10 or 30 mg purified pentachlorophenol/kg bw/day to groups of 27 male and 27 female Sprague-Dawley rats for 22 or 24 months, respectively. The pentachlorophenol used in this study was representative of DOWICIDE EC-7, a commercially available pentachlorophenol, and chemical analyses yielded the following composition based on four replicates: pentachlorophenol, 90.4±1.0%; tetrachlorophenol, 10.4±0.2%; trichlorophenol, <0.1%; 2,3,7,8-tetrachlorodibenzo-p-dioxin (DD), <0.05 ppm; hexachloro-DD, 1.0±0.1 ppm; heptachloro-DD, 6.5±1.0 ppm; octachloro-DD, 15.0±3.0 ppm; hexachlorodibenzofuran (DF), 3.4±0.4 ppm; heptachloro-DF, 1.8±0.3 ppm; octachloro-DF, <1; hexachlorobenzene, 400±40 ppm. Changes in body weight, food consumption and overt behavior were recorded monthly. No data on

mortality rates for the dose groups are provided. At the termination of the study, the observations made included hematology, clinical chemistry, urinalysis, organ weights and gross and microscopic examination of tissues. Decreased body weight gain was observed in females receiving 30 mg/kg bw/day (mean of 428 g in controls vs. 378 g in treated during last 12 months of the study). This dose also resulted in an increased urine specific gravity in females and increased serum glutamic pyruvic transaminase (SGPT) activity in both sexes (males-control 38±16, treated 63±13; females-control 36±8, treated 48±15). Pigmentation of the liver and kidneys was observed in females receiving 10 (8/27-liver, 7/29-kidney) or 30 (16/27-liver, 19/27-kidney) mg/kg bw/day and in males receiving 30 mg/kg bw/day (1/27-liver).

Greichus et al. (1979) administered oral doses of 0, 5, 10 or 15 mg purified pentachlorophenol/kg bw/day to four groups of six pigs for 30 days. Vehicle control received daily capsules of pure lactose. Weight gain was measured weekly, blood chemistry values were determined at the beginning, middle and end of the study, and microscopic examinations were made on the liver, kidneys, spleen, brain and muscles at the end of the study. No differences in weight gain or feed consumption were observed in any of the groups. Liver weights were increased in the 10 and 15 mg/kg bw/day groups. The only histologic finding was a diffuse cloudy swelling of the hepatocytes in the treated pigs (specific groups not identified).

Target Organ Toxicity

Based on the studies reported previously, the major target organs for systemic pentachlorophenol exposure appear to be the liver, kidneys and central nervous system. Dermal administration also results in toxic effects at the site of application.

Hepatic Effects. Pentachlorophenol appears to be an inducer of hepatic mixed-function oxidase. Vizethum and Goerz (1979) fed female Wistar rats diets containing 0.05% purified pentachlorophenol (500 mg/kg diet) for 2 weeks. This treatment resulted in a significant ($p<0.05$) increase of both the content and activity of cytochrome P-450 in microsomes and the nuclear membranes.

Technical grade pentachlorophenol has been demonstrated to produce a variety of hepatic effects. Fleischer et al. (1980) administered 30 mg technical grade pentachlorophenol/kg bw/day to male Wistar rats for 15 consecutive days by i.p. injection. The livers were excised and examined by light and electron microscopy 24 hours after the last injection. Light microscopy revealed enlargement of the sinusoids accompanied by activation of the Kuppfer cells, a larger heterochromatin/euchromatin ratio, and an increase in the number of nucleoli in the hepatocytes (20.59%, $p<0.001$). At the level of the electron microscope, mitochondria were found to be reduced in size and pleomorphic. Occasional swelling and clearing of the matrix and cristolysis were seen. There was a pronounced proliferation of the smooth endoplasmic reticulum, with the greatest increase occurring around the bile canaliculi.

Purified pentachlorophenol appears to produce less severe hepatic effects than does the technical grade. Kimbrough and Linder (1978) investigated the effects of technical and purified pentachlorophenol on rat liver. Diets containing 0, 20, 100 or 500 ppm (0, 20, 100 or 500 mg/kg diet) were fed to Sherman rats for 8 months. At a dietary concentration of 500 ppm, purified pentachlorophenol resulted in slightly enlarged liver

cells with occasional eosinophilic cytoplasmic inclusions. Technical grade pentachlorophenol produced such alterations in hepatic morphology at all doses tested.

Schwetz et al. (1978) fed male and female Sprague-Dawley rats for up to 24 months on diets that resulted in doses of 1, 3, 10 or 30 mg pentachlorophenol/kg bw/day. The specific composition of the compound is presented at the end of the General Toxicity Section. In the two high-dose groups, a dose-related incidence of dark discolored livers were noted at necropsy. Microscopic examination revealed brown granular pigment within hepatocytes and reticuloendothelial cells surrounding the central vein in 1/27 livers from the high dose males, 8/27 livers from females receiving 10 mg/kg bw/day and 16/27 livers from females receiving 30 mg/kg bw/day.

Since inhibition of cellular respiration is believed to be a major mechanism by which pentachlorophenol induces its toxic effect (see the Uncoupling of Oxidative Phosphorylation Section in Chapter 7), Gotz et al. (1980) investigated the effect of purified pentachlorophenol on cellular respiration and transport of sulfobromophthalein in isolated rat hepatocytes. At concentrations of 4 μM or more, pentachlorophenol inhibited the secretion of the sulfobromophthalein-glutathione conjugate. At a concentration of 5 μM, mitochondrial respiration was completely uncoupled.

Renal Effects. Johnson et al. (1973) maintained Sprague-Dawley rats on diets that provided 1, 3, 10 or 30 mg pentachlorophenol/kg bw/day for 90 days. Purified pentachlorophenol produced increases in kidney and liver

weight at a dose of 30 mg/kg bw/day. Commercial grade pentachlorophenol produced increases in kidney weight at doses as low as 3 mg/kg bw/day.

Schwetz et al. (1978) examined the histological effects of Dowicide EC-7 antimicrobial, a semipurified pentachlorophenol, on kidney tissue. Groups of 27 male and 27 female Sprague-Dawley rats were maintained on diets that provided 0, 1, 3, 10 or 30 mg pentachlorophenol/kg bw/day for 22-24 months. A dose-related incidence (7/27 in 10 mg/kg group; 19/27 in 30 mg/kg group) of an unidentified brown granular pigment was observed within the tubular epithelial cells of the females.

Central Nervous System Effects. The central nervous system appears to be a major target for pentachlorophenol toxicity. McGavack et al. (1941) administered s.c. doses of 1/20, 1/10 or 1/4 of the minimum lethal dose (276 mg/kg bw) of pentachlorophenol (purity unspecified) daily for up to 60 days. A number of central nervous system lesions were observed in all dose groups, including capillary congestion, slight chromatolysis of nerve cells, diffuse focal areas of perivascular lymphocytic and mononuclear infiltration, and circumscribed subpial collections of unspecified small round cells. Gross symptoms (muscular weakness and convulsive seizures) observed following a lethal dose of pentachlorophenol are also consistent with toxic effects on the nervous system.

Other Effects

Carcinogenicity. The National Toxicology Program is currently testing technical grade pentachlorophenol and a commercial pentachlorophenol product, Dowicide EC-7, for carcinogenic activity (NTP, 1983). No data from these studies are currently available.

Commercial grade pentachlorophenol, Dowicide-7, has been tested for carcinogenicity in (C57BL/6 x C3H/Anf)F_1 and (C57BL/6 x AKR)F_1 mice (BRL, 1968a). For each strain, groups of 18 male and 18 female mice were administered 46.4 mg pentachlorophenol/kg bw/day by gavage from day 7-28 postpartum. The mice were then transfered to diets containing 130 ppm (130 mg/kg diet) pentachlorophenol for the next 78 weeks. Survival was ~50% in all treated groups. Controls consisted of 79-90 mice of each sex and strain which had either been untreated or had received only the carrier, gelatin. In the same study, identical groups of mice were administered single s.c. injections of 46.4 mg pentachlorophenol/kg bw in corn oil at age 28 days. There were no statistically significant differences in tumor incidence between treated and control groups.

Schwetz et al. (1978) investigated the carcinogenicity of a commercial grade of pentachlorophenol (described on p. V-12) in Sprague-Dawley rats. Groups of 27 rats of each sex were fed diets containing pentachlorophenol at concentrations that resulted in doses of 0, 1, 3, 10 or 30 mg/kg bw/day for a total of 22-24 months. No significant increase in total or specific types of tumors was found when the treated animals were compared with controls. Survival between groups was similar.

In other studies, Catilina et al. (1981) tested both purified and technical grades of pentachlorophenol (6 mg/kg bw/dose) for carcinogenicity in Wistar rats. The pentachlorophenol was administered by s.c. injection, 3 times/week for 40 weeks. No evidence of carcinogenicity was observed after a 30-month, posttreatment observation period; however, transient alterations in blood cell counts were noted in the groups receiving purified pentachlorophenol.

In an initiation/promotion study, commercial grade pentachlorophenol was not found to be a promotor of skin carcinogenesis (Boutwell and Bosch, 1959). A single application of 75 µg DMBA (0.3% in benzene) was applied to the backs of thirty-five 2- to 3-month-old Sutter mice. After a 1-week recovery period, twice weekly applications of 25 µg pentachlorophenol in benzene were begun and continued for 14 weeks. The mice were then observed for the remainder of the 24-month study. No promotion of tumor development was detected.

Mutagenicity. The mutagenicity of pentachlorophenol in prokaryotic organisms is summarized in Table V-3. In a large number of assays, pentachlorophenol failed to produce mutations in Salmonella typhimurium, Escherichia coli or Serratia marcescens, either with or without activation by mammalian S-9 mixtures.

Fahrig (1974) and Fahrig et al. (1978) reported positive results for the induction of forward mutations in Saccharomyces cerevisiae at concentrations as low as 0.19 mM (50 mg/ℓ). Negative results were obtained when intragenic or intergenic recombination were used as the endpoints.

Positive results have also been obtained in the Bacillus subtilis rec assay (Shirasu, 1976; Waters et al., 1982). Shirasu (1976) reported weakly positive results using strains H17Rec^{+} and M45Rec^{-} with a dose of 5 µg/plate. Waters et al. (1982) tested six unspecified concentrations, with a maximum concentration of 10 mg/plate. Positive results were obtained, but no information on dose-response was reported.

TABLE V-3

Mutagenicity of Pentachlorophenol in Prokaryotic Organisms

Type of Test	Species	Strain	Dose	Purity	Result	S-9	Comments	Reference
Spot	S. typhimurium	8 NS	NA	commercial	-	-		Anderson et al., 1972
Plate incorporation	S. typhimurium	TA1535, TA1537, TA1538, TA98 and TA100	up to 5 mg/plate	NS	-	+/-		Simmon et al., 1977
Liquid Suspension	S. typhimurium	TA1535, TA1537, TA1538, TA98 and TA100	NS	NS	-	+/-		Simmon et al., 1977
Vapor	S. typhimurium	TA1535, TA1537, TA1538, TA98 and TA100	NA	NS	-	+/-		Simmon et al., 1977
Spot	S. typhimurium	LT-2	NA	NS	-	-		Lemma and Ames, 1975
Plate incorporation	S. typhimurium	TA100, TA98, TA1535, TA1537 and TA1538	up to 5 mg/plate	commercial	-	+/-		Moriya et al., 1983
Plate incorporation	S. typhimurium	TA1535, TA1537, TA1538, TA98 and TA100	up to 10 mg/plate	technical	-	+/-		Waters et al., 1982
Host mediated	S. typhimurium	G46	NS	NS	-	NA		Buselmaier et al., 1973
Host mediated	S. marcescens	a21	NS	NS	-	NA		Buselmaier et al., 1973
Spot	S. marcescens	a21, a742	NA	NS	-	-		Fahrig, 1974
Plate incorporation	E. coli	WP2uvr⁻	up to 5 mg/plate	NS	-	+/-		Simmon et al., 1977
Liquid suspension	E. coli	NS	NS	NS	-	-		Fahrig, 1974
Plate incorporation	E. coli	WP2hcr	up to 5 mg/plate	NS	-	+/-		Moriya et al., 1983
Plate incorporation	E. coli	WP2uvrA	up to 10 mg/plate	technical	-	+/-		Waters et al., 1982
Spot	E. coli	p3478, W3100	up to 10 mg	technical	-	-		Waters et al., 1982

TABLE V-3 (cont.)

Type of Test	Species	Strain	Dose	Purity	Result	S-9	Comments	Reference
Rec	B. subtilis	M45, H17	up to 10 mg/plate	technical	+	-		Waters et al., 1982
Rec	B. subtilis	H17Rec$^+$, M45rec$^-$	5 µg/plate	NS	±	-	Weakly positive results	Shirasu, 1976
Liquid suspension	S. cerevisiae	D3	NS	NS	-	+/-		Simmon et al., 1977
Liquid suspension	S. cerevisiae	MP-1	400 mg/L	purified	+	-	Positive for forward mutation, negative for intragenic and intergenic recombination	Fahrig et al., 1978
Liquid suspension	S. cerevisiae	aAeZ, trp5	0.19 mM	NS	+	-		Fahrig, 1974

NA = Not applicable; NS = Not specified

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In other *in vitro* tests, pentachlorophenol produced a slight increase in chromosomal aberrations in human lymphocytes (Fahrig, 1974). The test system used by Fahrig is only capable of detecting short-term effects; therefore, based on the data presented in the report, the statistical significance of this increase cannot be determined.

Pentachlorophenol has also been tested for mutagenicity in the *Drosophila melanogaster* sex-linked recessive lethal test (Fahrig, 1974; Fahrig et al., 1978; Vogel and Chandler, 1974). The concentration used was not specified in the studies by Fahrig et al. (1978), but Vogel and Chandler (1974) used a concentration of 7 mM in the media. No increase in sex-linked recessive lethals was reported in either study.

Only one study has been reported in which the mutagenicity of pentachlorophenol was tested in a mammalian species. Fahrig et al. (1978) bred female C57BL/6JHan mice to fertile males of a rotation bred T-stock, yielding embryos that were heterozygous for four different coat-color genes. On day 10 of gestation, the dams were administered a single i.p. injection of either 50 or 100 mg purified pentachlorophenol/kg bw. The pups were checked for color spots twice a week between the ages of 2 and 5 weeks postpartum. Under these conditions, 9 of 473 pups evidenced color spots in their fur, 4 of which were considered to be definite indications of mutation. One gray color spot and one light brown color spot were observed in the 50 mg/kg dose group. One light gray and one gray color spot were seen in the 100 mg/kg group. In the controls, only 1 of 967 pups had a color spot definitely resulting from mutation. Fahrig et al. (1978) concluded these changes were evidence of definite but weak mutagenic activity.

Only limited information is available on the in vivo mutagenicity of pentachlorophenol in humans. Wyllie et al. (1975) investigated the induction of chromosomal aberrations in workers at a wood-treatment plant in Idaho. During the 5-month study period, the average monthly air concentrations ranged from 263.0-1887.9 ng/m³. Peripheral blood cells were cultured and 25 cells from each culture (6 exposed, 4 control samples) were scored for chromosome number, abnormal configurations, breaks and gaps. No statistically significant differences were observed between control and exposed groups; however, the number of breaks and gaps was consistently higher in exposed groups as compared with control groups.

Teratogenicity. A number of investigators have studied the teratogenicity of pentachlorophenol in rats. Larsen et al. (1975) investigated the teratogenicity of purified pentachlorophenol (60 mg/kg bw) in CD rats (6 dams/group). A single dose was administered by gavage on day 8, 9, 10, 11, 12 or 13 of gestation. The incidence of resorptions in the treated groups was not significantly greater than that in controls. The authors concluded that the number of rats with malformations (4) was minimal and could have been due to maternal toxic effects; however, 3 (exencephaly, microphthalmia, and absent tail) of the 4 observed malformations occurred in litters exposed on day 9 of gestation. The fourth, dwarfism occurred in a rat exposed on day 8. Treatment on day 9 or 10 of gestation also resulted in a significant ($p<0.05$) reduction in fetal weight gain (20 and 13%) with the greatest reduction occurring following treatment on day 9.

Schwetz and Gehring (1973) and Schwetz et al. (1974b) administered daily oral doses of both commercial (88% pure) and purified (>98% pure) pentachlorophenol in corn oil to 20 Sprague-Dawley rats per group on days

6-15 of gestation at doses of 0, 5, 15, 30 and 50 mg/kg/day. The maximum tolerated dose to dams in these studies was 50 mg commercial pentachlorophenol/kg bw/day. A dose-related fetotoxicity ($p<0.05$ increased number of resorptions in each treated group, decreased fetal body weight with 2 top doses, increased incidences of subcutaneous edema, skeletal anomalies in fetuses in the 2 top dose groups and increased incidence of dilated ureters in fetuses in the top dose group) was reported. Maternal body weight gain was lower ($p<0.05$) with the two highest doses. The purified pentachlorophenol was slightly more toxic as evidenced by effects on maternal weight gain (significant $p<0.05$ decreases in top two dose groups), fetal body weight and crown-rump length ($p<0.05$ decrease with the high dose), fetal anomalies and resorptions (increased $p<0.05$ in two top dose groups) than the commercial product. The authors included anomalies of the skull, ribs, vertebrae and sternebrae as well as subcutaneous edema, all of which were increased ($p<0.05$) in the highest dose groups, as signs of fetotoxicity rather than teratogenicity. Delayed ossification of the fetal skull was also increased ($p<0.05$) in incidence in the low dose group. The sex ratio of the surviving pups was significantly ($p<0.05$) altered by a dose of 50 mg commercial pentachlorophenol/kg bw/day, M:F of 79:21, and a dose of 30 mg purified pentachlorophenol/kg bw/day, M:F of 83:17. Additional groups of rats were given corn oil alone or 30 mg/kg of either commercial or purified pentachlorophenol in corn oil on gestation days 8 through 11 or 12 through 15. The fetus was more susceptible to the toxic action of pentachlorophenol (both commercial and purified) during early organogenesis (days 8-11). Both pentachlorophenol products induced decreased ($p<0.05$) maternal weight gain and increased ($p<0.05$) incidences of subcutaneous edema and skeletal anomalies in fetuses exposed during gestation days 8-11. Purified pentachloro-

phenol also increased ($p<0.05$) the incidence of resorptions when given on days 8-11 and subcutaneous edema and sternebral anomalies when given on days 12-15. Commercial pentachlorophenol also increased ($p<0.05$) the incidence of fetal skeletal anomalies. Fetal body weight and crown-rump length were decreased ($p<0.05$) when both products were given on days 8-11 and when purified was given on days 12-15.

The authors concluded that 5 mg/kg bw/day was a NOEL for the commercial grade of pentachlorophenol. However, the conclusion in the U.S. EPA Position Document 4 (U.S. EPA, 1984) is that this study did not establish a fetotoxicity NOEL for either grade of pentachlorophenol, and the Agency concluded that 3 mg/kg bw/day could be considered a NOEL for pentachlorophenol's fetotoxicity.

Larsen et al. (1975) administered a single oral dose of uniformly labeled [^{14}C]pentachlorophenol (60 mg/kg bw) to CD rats on day 15 of gestation. Analysis of radioactivity indicated that only negligible amounts of pentachlorophenol crossed the placental barrier. These data, combined with the observation that treatment on days 9 and 10 of gestation resulted in the greatest effects on rats, indicate that transport by the yolk-sac may be a significant factor in the fetotoxic response of rodents to pentachlorophenol.

One study has been reported in which the teratogenicity of pentachlorophenol in mice was assayed (BRL, 1968b). Commercial pentachlorophenol, Dowicide-7, was tested for teratogenicity in six litters of BL6 mice. A dose of 25 mg/kg bw in dimethylsulfoxide was administered by s.c. injection

on days 6-14 of gestation. No increases in fetal mortality or terata were reported in this study.

The only other species in which pentachlorophenol has been tested for teratogenicity is the Golden Syrian hamster (Hinkle, 1973). Daily oral doses of 1.25-20 mg pentachlorophenol (purity unspecified)/kg bw/day were administered on days 5-10 of gestation. An increase in fetal deaths and resorptions (or both) were reported in 3 of 6 test groups; however, no details were given in the abstract. A more detailed publication of this study has not been encountered in the literature.

Two groups have studied the effects of longer-term exposures on reproductive function and fetal development. Schwetz et al. (1978) fed groups of 10 male and 20 female Sprague-Dawley rats on diets that resulted in a dose of 0, 3 or 30 mg pentachlorophenol (described on p. V-12) kg bw/day for 62 days before mating, during the mating period and throughout gestation and lactation. A dose of 3 mg/kg bw/day produced no measurable effect; however, a dose of 30 mg/kg bw/day resulted in a significant ($p<0.05$) reduction in neonatal body weight over the 21-day observation period (75% of controls at day 21), a decreased percentage of live births (93% of controls, $p<0.05$), and decreased survival of the pups at days 7, 14 and 21 (80% of controls at day 21). The significant increase ($p<0.05$) in lumbar spurs and vertebrae with unfused centra in high-dose litters was attributed to perinatal toxicity. The 30 mg/kg bw/day dose also resulted in a significant decrease (90% of controls $p<0.05$) in maternal body weight, on day 21 postpartum indicating that maternal toxicity may have influenced the fetotoxic effects observed.

Exon and Koller (1982, 1983a,b) fed groups of 12-20 female Sprague-Dawley rats on diets containing 0, 5, 50 or 500 ppm (0, 5, 50 or 500 mg/kg diet) pentachlorophenol (95% purity by manufacturer; reanalysis indicated 85.5% purity) from weaning at 21 days of age through breeding at 90 days and continuing until the pups were weaned at 3 weeks postpartum. Some of the pups were continued on pentachlorophenol-containing diets for an additional 10 weeks. A dose-related but not statistically significant increase in conception rate was observed in all treatment groups. Pentachlorophenol produced significant effects (data were not presented) on the immune system, as indicated by decreased antibody titers, decreased delayed-type hypersensitivity and increased peritoneal macrophage numbers. Pentachlorophenol also reduced the latency of ethylnitrosourea-induced transplacental carcinogenesis. No statistically significant effects were observed on red or white blood cell counts, packed cell volume, hemoglobin levels, mean corpuscular volume, litter size, birth weight, weight at weaning or survival to weaning.

Summary

Acute exposure of experimental mammals to pentachlorophenol results in an initial rise in body temperature and respiration rate. Respiration then becomes slower and dyspneic as coma develops. Death is characterized by cardiac and muscular collapse with terminal asphyxial convulsions. An immediate and pronounced rigor mortis is often noted. Oral LD_{50}s ranging from 27->300 mg/kg bw have been reported (see Table V-1), with no species being noticeably more susceptible than any other. The lower LD_{50} values tend to be found in the older literature and probably reflect a high degree of contamination by chlorinated dibenzo-p-dioxins and dibenzofurans. There are indications that tolerance to pentachlorophenol toxicity develops with prolonged exposure to the compound (Deichmann et al., 1942).

A wide variety of symptoms have been reported following subchronic oral administration (60 days) of pentachlorophenol, including secondary anemia, leukopenia, polycythemia, increased blood sugar levels, heart dilation, hemorrhages and congestion in the lungs and kidneys, hypertrophy of the pulmonary artery, cloudy swelling of the liver, degenerative changes in the kidney tubules, and numerous lesions of the brain and spinal cord (McGavack et al., 1941). Dermal application also results in local irritation (Deichmann et al., 1942). Commercial pentachlorophenol containing chlorinated dibenzo-p-dioxins and dibenzofurans has been shown to be more toxic than purified pentachlorophenol in recent subchronic animal studies (Goldstein et al., 1977; Johnson et al., 1973).

Based on these studies, the major targets of pentachlorophenol toxicity seem to be the liver, kidneys and central nervous system. In the liver, pentachlorophenol produces pigmentation, increases liver weight and induces hepatic enzymes (Johnson et al., 1973; Schwetz et al., 1978). Effects on mitochondrial structure and cellular respiration have also been reported (Fleischer et al., 1980; Gotz et al., 1980). The major renal effects of purified pentachlorophenol have been reported to be increased kidney weight (Johnson et al., 1973) and pigmentation (Schwetz et al., 1978). Reported effects on the central nervous system have included capillary congestion, chromatolysis of the nerve cells, diffuse focal areas of perivascular lymphocytes and mononuclear infiltration, and circumscribed subpial collections of unspecified small, round cells (McGavack et al., 1941).

Pentachlorophenol has not been shown to be carcinogenic in a number of studies (BRL, 1968a; IARC, 1979; Schwetz et al., 1978; Catilina et al., 1981). It has also produced negative results in an initiation/promotion study (Boutwell and Bosch, 1959). These results are consistent with mutagenicity studies of pentachlorophenol, the majority of which failed to demonstrate mutagenicity.

A number of teratogenicity studies have failed to clearly establish a teratogenic potential for pentachlorophenol, though fetotoxic effects have been detected (Larsen et al., 1975; Hinkle, 1973). Female rat fetuses were more sensitive than males to the fetotoxic effects of a maternal dose of 30 mg/kg bw/day (Schwetz and Gehring, 1973; Schwetz et al., 1974). The effects on the fetus may be a reflection of maternal toxicity, since the effects were observed at doses causing signs of maternal toxicity and the placental barrier seems to be impermeable to pentachlorophenol (Larsen et al., 1975). The rat fetus appears to be more susceptible to pentachlorophenol fetotoxicity during early gestation in that Larsen et al. (1975) found the strongest fetal effect when pentachlorophenol was given on gestation day 9 or 10 and Schwetz et al. (1974) found greater fetotoxicity when pentachlorophenol was given on days 8-11 compared to days 12-15 of gestation.

VI. HEALTH EFFECTS ON HUMANS

Clinical Case Studies

Nonfatal Exposures. Repeated exposure of the skin to sodium pentachlorophenate may produce dermatitis, systemic intoxication, and, in a limited number of people, an allergic response. Contact with the eyes can produce corneal damage, resulting in permanent impairment of vision (Dow Chemical Co., 1969a).

Acute toxicity has been reported in a number of studies following occupational exposure to pentachlorophenol. While these cases resulted from acute exposures, some of the symptoms may be related to chronic exposure at work.

Bergner et al. (1965) investigated four cases of nonfatal poisoning among factory workers at a Winnipeg plant. The major clinical symptoms observed were sweating, weight loss and gastrointestinal complaints.

Gordon (1956) reported four cases of nonfatal poisoning among herbicide sprayers in Australia. The onset of symptoms was characterized by abdominal pain, nausea and vomiting, with a profuse sweating developing shortly thereafter. In one case where the exposure occurred over a period of months, hepatic enlargement with possible reversible toxic myocarditis was observed.

Baader and Bauer (1951) investigated health complaints among workers involved in the production of pentachlorophenol in a West German plant. Reported complaints included severe skin eruptions, furunculosis, neuralgic pain and bronchitis. From these descriptions, it is possible that many of

these symptoms resulted from dioxin contamination; however, the extent of contamination by chlorinated dibenzo-p-dioxins and dibenzofurans was not reported.

Other investigators have reported cases of acute poisoning following the home use of pentachlorophenol-containing products. These cases are less likely to involve chronic exposures than are the occupational exposures.

Chapman and Robson (1965) reported a case in which a 3-year-old girl was poisoned when an insecticide mixture contaminated the domestic water supply. Dermal contact was believed to be the major route of exposure. Symptoms included intermittent delirium, fever and convulsions. The clinical chemistry revealed acidosis, aminoaciduria and ketonuria. Her temperature returned to normal within 24 hours; however, aminoaciduria continued for 1 week.

Bevenue et al. (1967b) reported a case in which a male immersed his hands in a 0.4% pentachlorophenol solution for 10 minutes. The reported symptoms were localized redness and pain that persisted for 2 hours. Analysis of urine samples indicated that pentachlorophenol was absorbed through the intact skin and slowly excreted in the urine. After 3 weeks, urinary concentrations were still ~27% of the initial values.

Robson et al. (1969) and Armstrong et al. (1969) reported 20 cases of poisoning have also occurred following short-term exposure of neonates in a hospital nursery. These neonates evidenced signs of excessive sweating, tachycardia, tachypnea, respiratory distress, hepatic enlargement and

metabolic acidosis. In two of the infants who died, autopsy revealed fatty infiltration of the liver and fatty degeneration of the renal tubular cells. Exchange blood transfusion proved to be an effective treatment. Exposure was found to result from "percutaneous absorption of pentachlorophenol which had been used in the laundering of the diapers and the infants' bed linen."

Fatal Exposures. Three reports are available that describe the effects of fatal exposures in humans.

Bergner et al. (1965) described a case of pentachlorophenol intoxication in a 58-year-old male who had been employed for 1 week dipping wood into a petroleum solution which reportedly contained 4.1% pentachlorophenol and 0.9% other unspecified chlorophenols. The individual initially experienced anorexia, fatigue, sweating, and thirst. The individual died after developing a temperature of over 106°F. An autopsy revealed slight centrilobular degeneration of the liver and mild renal tubular degeneration.

Gordon (1956) reported five fatal cases of pentachlorophenol poisoning among herbicide sprayers in Australia. Death generally occurred within 24 hours, with a rapid change from a patient who is not remarkably sick to one who is completely moribund over the course of 1-2 hours. The observed symptoms were the same as in the nonfatal exposures.

Menon (1958) reported nine deaths over a period of 18 months among sawmill workers in Asia with known exposure to pentachlorophenol. Fever and profuse sweating were noted in all cases, but abdominal symptoms were much less severe than was reported by Gordon (1956). Severe terminal spasms occurred in all cases.

Epidemiological Studies

The effects of chronic occupational exposure to pentachlorophenol have been reported in a series of epidemiological studies in Hawaii (Klemmer, 1972; Takahashi et al., 1976; Begley et al., 1977; Klemmer et al., 1980).

Klemmer (1972) reported a study involving adult males occupationally exposed in wood-treating plants or as farmers/pest control operators to pentachlorophenol in Hawaii. The study included "over 300" volunteers, of which 152 were active at the time of the report. SGOT, SGPT and LDH levels were found to be elevated following chronic pentachlorophenol exposure. In a follow-up study, Klemmer et al. (1980) reported that lowgrade infections or inflammations of the skin and subcutaneous tissue, protective membrane of the eyes and the mucosal membranes of the upper respiratory tract occurred to a significantly greater extent in exposed groups as compared with control groups. The authors reported the following mean serum levels of pentachlorophenol in groups exposed in wood-treatment plants: 0.32 ppm in 32 controls, 1.92 ppm in 24 workers exposed to PCP and other wood preservative chemicals, 3.78 ppm in 22 workers exposed to PCP only. The authors did not conclude that any rangible effects occurred with blood chemistry and urine analyses from PCP exposure.

Takahashi et al. (1976) investigated the effect of pentachlorophenol on plasma protein levels in an unspecified number of workers in Hawaii. Using stepwise multiple regression analysis, chronic exposure to pentachlorophenol significantly ($p<0.05$) increased gamma mobility C-reactive proteins which are often elevated in acute stages of inflammatory disorders or tissue

damage, total bilirubin, and creatine phosphokinase above the values observed in controls, although the latter two were considered to be within normal limits.

Begley et al. (1977) investigated the effect of pentachlorophenol on renal function among 18 workers at a Honolulu wood-treating plant. They found that creatinine clearance and phosphorus reabsorption were depressed, suggesting that pentachlorophenol reduces both glomerular filtration and tubular function. Both values demonstrated considerable improvement following a 20-day vacation, implying that these effects of pentachlorophenol on the kidney were reversible.

High Risk Subpopulations

The available data are insufficient to clearly identify a high-risk human subpopulation. Available data from animal experiments indicate that the fetus and neonatal animal are particularly susceptible to pentachlorophenol toxicity, although the available data suggest that pentachlorophenol has a low teratogenic potential. The toxic response of newborns to acute exposures at what were probably low levels of pentachlorophenol indicates that the neonatal period may represent a time of heightened risk for humans as well (Robson et al., 1969; Armstrong et al., 1969). However, current information, particularly on exposure, is inadequate for an assessment of the relative toxicity of pentachlorophenol between neonatal and adult humans.

Summary

Human exposure to pentachlorophenol results in local irritation, systemic effects, and, in a limited number of people, an allergic response (Dow Chemical Co., 1969a). Pentachlorophenol poisoning is characterized by a profuse sweating, often accompanied by fever, weight loss and gastrointestinal complaints (Bergner et al., 1965; Chapman and Robson, 1965; Gordon, 1956). Liver and kidney involvement have been indicated in cases of fatal poisoning (Robson et al., 1969; Armstrong et al., 1969).

Epidemiological studies have revealed effects following occupational exposure to pentachlorophenol. One group of subjects also had a significantly increased incidence of low-grade infections or inflammations (Klemmer et al., 1980). Kidney function is depressed during chronic exposure, but these effects are at least partially reversible (Begley et al., 1977).

VII. MECHANISMS OF TOXICITY

Uncoupling of Oxidative Phosphorylation

Gotz et al. (1980) determined the toxicity of pentachlorophenol in isolated rat hepatocytes, as measured by decreases in secretion of glutathione-sulfobromophthalein conjugates. The decreased secretion correlated with the uncoupling of mitochondrial respiration, implying that the hepatotoxic effects of pentachlorophenol may be due to an interference with the energy metabolism of the cell.

Weinbach and Garbus (1965) investigated the interaction of pentachlorophenol with rat liver mitochondria. They found that mitochondria could accumulate pentachlorophenol to concentrations greatly in excess of those necessary for the complete uncoupling of oxidative phosphorylation. Purified mitochondrial protein bound pentachlorophenol as well as the intact mitochondria, implying that "the protein-phenol interaction may be an important factor in the uncoupling phenomenon."

In contrast, Leighty and Fentiman (1982) proposed that the effect of pentachlorophenol on oxidative phosphorylation results from binding to fatty acids in the mitochondrial membrane. They demonstrated the formation of a pentachlorophenol-palmitic acid conjugate in a coenzyme A fortified, rat liver microsomal system.

Interactive Effects

Pentachlorophenol pretreatment has been demonstrated to alter the toxicity of carcinogenic hydroxamic acids that are activated through the formation of sulfate esters (Meerman et al., 1980; Meerman and Mulder, 1981).

N-hydroxy-2-acetylaminofluorene produces a periportal necrosis accompanied by increases in SGOT in male Wistar rats. A single i.p. dose of pentachlorophenol (40 μmol/kg bw), 45 minutes before administration of N-hydroxy-2-acetylaminofluorene, resulted in a complete inhibition of hepatotoxicity, presumably by the inhibition of N-O-sulfation (Meerman and Mulder, 1981).

Meerman et al. (1983) investigated the effect of repeated pentachlorophenol exposure on sulfation in male Wistar rats. The rats were fed diets containing 350 ppm (350 mg/kg diet, 17.5 mg/kg bw) sodium pentachlorophenolate or given drinking water containing 1.4 mM sodium pentachlorophenolate for 1 week. Both of these treatments resulted in a 30-45% decrease in the sulfation of harmol and a 70-75% inhibition of the sulfation of the carcinogenic arylhydroxamic acid, N-hydroxy-2-acetylaminofluorene.

Pentachlorophenol appears to inhibit sulfation at the level of the cytosolic sulfotransferase, but the mechanism of this inhibition has not been elucidated (Mulder and Scholtens, 1977).

Pentachlorophenol also interacts with the carcinogenic amino-azo dyes in ways that apparently do not involve inhibition of sulfation. N-methyl-4-aminoazobenzene is believed to be activated through formation of a sulfate ester, resulting in the formation of three major DNA adducts (Tullis et al., 1981). Pretreatment with pentachlorophenol preferentially inhibits the formation of the N^6-deoxyadenosine adduct, although all three adducts are presumably formed through the sulfate ester intermediate (Tullis and Kadlubar, 1983). The mechanism of this interaction is unknown at this time.

Exon and Koller (1983a) have investigated the effect of several chlorinated compounds on ethylnitrosourea-induced transplacental carcinogenesis. Unlike 2-chlorophenol, no cocarcinogenic effect of pentachlorophenol was detected; however, the time to tumor (data not given) was decreased. This may be a result of the effects of pentachlorophenol on the immune system described in the Chronic and Subchronic Toxicity Section in Chapter V.

Pentachlorophenol has also been demonstrated to be an inducer of hepatic microsomal enzymes (Vizethum and Goerz, 1979). This effect would be expected to alter the toxicity of a wide variety of exogenous compounds, but this effect has not been specifically demonstrated.

Summary

Pentachlorophenol is an uncoupler of cellular oxidation and phosphorylation, resulting in an increase in the basic metabolic rate. This uncoupling presumably results from the interaction of pentachlorophenol with mitochondrial protein (Weinbach and Garbus, 1965), though Leighty and Fentiman (1982) proposed that conjugation with fatty acids in the mitochondrial membrane may be involved.

Pentachlorophenol has been demonstrated to reduce the toxicity of N-hydroxy-2-acetylaminofluorene by the inhibition of cytosolic sulfotransferase (Meerman et al., 1980; Meerman and Mulder, 1981) and is presumed to alter the toxicity of a variety of toxicants by the induction of microsomal enzymes (Vizethum and Goerz, 1979). In addition, pentachlorophenol appears to alter the binding of N-methyl-4-aminoazobenzene to hepatic DNA by a mechanism other than inhibition of sulfation (Tullis and Kadlubar, 1983).

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the noncarcinogenic and carcinogenic effects. In the quantification of noncarcinogenic effects, an acceptable daily intake (ADI) is calculated. An adjusted acceptable daily intake (AADI) and health advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{\text{(NOAEL or LOAEL in mg/kg/day) (body weight in kg)}}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking water volume in } \ell\text{/day}} = \text{mg/}\ell$$

where: NOAEL = no-observed-adverse-effect level

LOAEL = lowest-observed-adverse-effect level

Body weight = 70 kg for adult or 10 kg for child

Drinking water volume = 2 ℓ/day for adults or 1 ℓ/day for children

Uncertainty/Safety Factor = 10, 100 or 1000

Utilizing these equations, the following drinking water concentrations are developed for noncarcinogenic effects:

1. A 1-day HA for 10 kg child
2. A 1-day HA for 70 kg adult
3. A 10-day HA for 10 kg child
4. A 10-day HA for 70 kg adult
5. A lifetime AADI for a 70 kg adult

The distinctions made between the HA calculations (items 1-4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited

period of exposure (possibly 1-2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon noncarcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivities to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS, 1977, 1980) are typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species.
- An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more species, but human data are not available.
- An uncertainty factor of 1000 is used when limited or incomplete acute or chronic toxicity data are available or when only the acute or chronic toxicity data identify a LOAEL (but not NOEL/NOAEL) for one or more species are available.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines (NRC, 1977) for selection of an uncertainty factor, but must be considered, include the following: 1) the quality of the toxicology data, 2) the significance of the adverse effect, and 3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen (there is insufficient evidence to classify pentachlorophenol as a carcinogen following oral exposure), mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical by drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans, these data must be converted to an equivalent human dose. This conversion includes correction for noncontinuous animal feeding, nonlifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 ℓ of water per day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as 1) incomplete knowledge concerning the health effects of contaminants in drinking water, 2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results, and 3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

In many of the studies reported in this review, either technical grade pentachlorophenol or pentachlorophenol of unknown purity was used. There were toxicological responses observed in these studies which may have resulted from or been enhanced by contamination with chlorinated dibenzo-p-dioxins and dibenzofurans (Goldstein et al., 1977). Consequently, studies in which purified grades of pentachlorophenol containing reduced levels of chlorinated dibenzo-p-dioxins and dibenzofurans were used are emphasized for the derivation of Health Advisories.

Existing Guidelines and Standards

Pentachlorophenol has been registered as a wood preservative since 1948. It is currently registered for agricultural use as a seed treatment for beans, alfalfa, clover, lespedeza and vetch, though the U.S. EPA has issued a notice of Rebuttable Presumption Against Registration (RPAR) for pesticide products containing pentachlorophenol (43 FR 48443-48477; 46 FR 13020). The ACGIH (1980, 1983) has established a threshold limit value (TLV) of 0.5 mg/m³ and a short-term exposure level (STEL) of 1.5 mg/m³ for dermal exposure. U.S. EPA (1980) recommended an ambient water quality criterion of either 1.01 mg/ℓ based on the toxicity or 0.030 mg/ℓ based on the organoleptic properties of pentachlorophenol. The NAS (1977) calculated a safe drinking water level of 0.021 mg/ℓ using the 90-day toxicity study in rats by Johnson et al. (1973) and a 1000-fold uncertainty factor. The WHO (1984) has recommended a drinking water criterion of 10 µg PCP/ℓ.

Noncarcinogenic Effects

1-Day Health Advisory. The data considered usable for the derivation of a 1-day HA are summarized in Table VIII-1. As can be seen from this table, these data are essentially confined to acute or short-term toxicity studies done with rats.

The study by Nishimura et al. (1982) provides a dose range indicating a dose producing no effect and doses producing effects, namely in the liver, after a single oral treatment. Sodium pentachlorophenate instead of pentachlorophenol, which was the test material used in other studies considered for HAs, was evaluated in this study. However, this study utilizes a dosing

TABLE VIII-1

Effects of Acute Exposure to Purified Pentachlorophenol

Species	Route	Duration of Exposure	Dose (mg/kg bw/day)	Severity Level	Effects	Reference
Rat	oral	1 day	60	LOAEL	Reduced fetal weight when administered on day 9 or 10 of gestation.	Larsen et al., 1975
Rat	oral	1 day	10[a]	NOEL	No effect on liver weight.	Nishimura et al., 1982
			30	NOAEL (LOEL)	Increased liver-to-body weight ratio	
			60	NOAEL	Highest dose which did not result in increased hepatic glycogen levels.	
			120	LOAEL	Lowest dose which produced a significant increase in hepatic glycogen levels.	
Rat	oral	10 days	5	NOAEL (LOEL)	Delayed ossification of the skull, but no skeletal or soft-tissue anomalies.	Schwetz and Gehring, 1973; Schwetz et al., 1974
			15	LOAEL	Skeletal and soft-tissue anomalies in the fetus.	
			30	FEL	Fetotoxicity, altered sex ratio, skeletal and soft-tissue anomalies in the fetus.	
Rat	oral	7 days	17.5[b]	NOAEL	Inhibition of hepatic sulfotransferases.	Meerman et al., 1983
Rat	i.p.	15 days	30	FEL	Enlargement of the sinusoids, increased heterochromatin/euchromatin ratios, increased number of nucleoli/hepatocyte. Altered mitochondrial morphology.	Fleisher et al., 1980
Mouse	oral	1 day	5	NOEL	Altered intestinal absorption of D-glucose. This is a free-standing NOEL. No dose was reported at which pure pentachlorophenol altered intestinal absorption.	Madge, 1981

[a]Sodium pentachlorophenate was the test material. Doses were indicated as pentachlorophenol by the authors.

[b]Sodium pentachlorophenate was the test material.

regimen closest to that expected with a 1-day exposure to humans, and the target organ effect is a toxicological endpoint applicable to both a 10 kg child and a 70 kg adult.

The liver effect at the lower doses in the Nishimura et al. (1982) study was confined to an increase in liver-to-body weight ratio, and this particular endpoint is identified as a NOAEL (LOEL) in that there could be a question of whether increased liver-to-body weight ratio by itself is an adverse toxicological effect (the authors suggested that it could be due to an increase in cell mass). However, the 10 mg/kg dose in the Nishimura et al. (1982) study did not induce any observable effect (NOEL). The study by Larson et al. (1975) suggests that the fetotoxicity of pentachlorophenol may not be as severe in rats when given for 1 day during organogenesis instead of during longer periods of organogenesis, but further investigation of this comparison is needed.

Although the effect levels are lower in the teratology study by Schwetz and Gehring (1973) and Schwetz et al. (1974b) than in the study by Nishimura et al. (1982), the 5 mg/kg and 15 mg/kg treatments in the teratology study were administered over the entire period of organogenesis (days 6-15), in contrast to the single dose administered by Nishimura et al. (1982). Although 30 mg/kg produced similar fetotoxicity whether given during gestation days 6-15 or 8-11 in these studies, lower doses were tested only during the longer period of gestation (days 6-15). The 10-day HA subsequently described would more closely approximate the repeated dosing pattern used in the teratology studies, and the no-effect level used in the 10-day HA calculation is below the lowest dose level used in the teratology studies.

Furthermore, in contrast to the fetal skeletal effects noted in the teratology study by Schwetz and associates (where dams were dosed by gavage during organogenesis), the reproduction study by Schwetz et al. (1978), discussed below, produced skeletal anomalies in weanling rats necropsied on day 21 of lactation, after treatment throughout gestation and lactation when dams were administered 30 mg/kg but not 3 mg/kg of pentachlorophenol in the diet. Schwetz et al. (1974b) concluded that a commercial grade of pentachlorophenol (88% pure) did not produce fetotoxicity at a dose level of 5.8 mg/kg with the same protocol used for testing purified pentachlorophenol (98%+ pure) in their teratology study. There may be a question as to whether the single effect of delayed skull ossification with 5 mg/kg of purified pentachlorophenol is a NOAEL (LOEL) or a LOAEL in view of the investigators' conclusion that this specific effect reflects a "mild non-specific toxicity without definite consequence" (Schwetz et al., 1974a) and the Agency conclusion in Position Document 4 (U.S. EPA, 1984) that a NOEL was not established for either grade of pentachlorphenol in this study. However, considering that fetal effects were not evident with a lower dose level of commercial pentachlorophenol in the reproduction study by Schwetz et al. (1978), the 1-day and 10-day HAs are considered to be consistent with the toxicity data as discussed herein.

10-Day Health Advisory. The studies considered in deriving the 10-day HA are summarized in Table VIII-2. The study by Schwetz et al. (1978) used a commercial purified grade of pentachlorophenol that contained the following components: chlorinated phenols, penta- (90.4%), tetra- (10.4%), tri- (<0.01%); dibenzo-p-dioxins, 2,3,7,8-tetrachloro- (<0.05 ppm), hexachloro- (1.0 ppm), heptachloro- (6.5 ppm), octachloro- (15.0 ppm);

TABLE VIII-2

Effects of Short-Term Oral Exposure to Purified Pentachlorophenol

Species	Duration of Exposure	Dose (mg/kg bw/day)	Severity Level	Effects	Reference
Rat	90 days	3	NOEL	No increase in liver or kidney weight.	Johnson et al., 1973
		10	NOAEL	Increased liver weight, but no effect on kidney weight.	
		30	LOAEL	Increased liver and kidney weights. No pathologic changes at any dose level.	
Rat	~110 days	3	NOAEL	No statistically significant effects, but observations were consistently intermediate between control and 30 mg/kg bw/day groups.	Schwetz et al., 1978
		30	FEL	Reduced neonatal body weight, decreased percentage of live births, decreased survival of pups, decreased maternal body weight.	
Mouse	10-19 weeks	6.5	FEL	Enhanced development of splenic tumors following challenge with Maloney sarcoma virus transformed cells.	Kerkvliet et al., 1982a,b
Pig	30 days	5	NOEL	No effects on blood chemistry, organ weights or pathology of liver, kidney, spleen, brain and muscle.	Greichus et al., 1979
		10	NOAEL	Increased liver weight.	

dibenzofurans, hexachloro- (3.4 ppm), heptachloro- (1.8 ppm), octachloro- (<1.0 ppm); hexachlorobenzene (400 ppm). The data summarized in Table VIII-2 from the study by Johnson et al. (1973) are for a chemically pure pentachlorophenol which contained no detectable level of any chlorinated dioxins. Greichus et al. (1979) used a purified pentachlorophenol for which their analysis of contaminants indicated 4.7% tetrachlorophenol, and 3.2 ppm total octachlorodibenzo-p-dioxins and furans. Independent analysis of this sample by Dow Chemical Company gave 0.98% tetrachlorophenol, and 0.4, 3.6 and 2.4 ppm of combined hexa-, hepta- and octachlorodibenzo-p-dioxins and dibenzofurans, respectively.

The results of these studies essentially show no or only minimal effects at doses ≤10 mg/kg/day. The practical significance of the observations by Kerkvliet et al. (1982a,b) of enhanced development of splenic tumors in mice may be questioned. The increased liver weight without pathological change at the 10 mg/kg dose in the Johnson et al. (1973) study is identified as a NOAEL (LOEL) in that there could be a question of whether increased liver weight by itself is an adverse toxicological effect. However, the studies by Johnson et al. (1973) and Schwetz et al. (1978) resulted in the same NOEL (3 mg/kg/day) for different toxicological endpoints as well as effect levels at higher doses under the conditions of the studies. Johnson et al. (1973) obtained similar results with their "improved grade" of pentachlorophenol as described previously in Table V-2. Therefore, the studies by Johnson et al. (1973) and Schwetz et al. (1978) provide a consistent basis for calculating a 10-day HA. Additionally, the NAS (1977) used the 3 mg/kg NOEL in the Johnson et al. (1973) study for a pentachlorophenol ADI calculation. The study by Greichus et al. (1979) showing a slightly higher NOEL of 5 mg/kg in

pigs, given pentachlorophenol as a bolus in capsules, supports the effect on liver weight found in rats by Johnson et al. (1973).

Lifetime Adjusted Acceptable Daily Intake (AADI). The studies from which the lifetime AADI can be derived are summarized in Table VIII-3. As can be seen from this table, the only species in which the effects of long-term exposure to pure pentachlorophenol have been studied is the rat. The study by Catilina et al. (1981) involves s.c. dosing and is, therefore, of limited use in the derivation of a HA for drinking water.

The purity of the pentachlorophenol used in the study by Schwetz et al. (1978) has been described in the 10-Day Health Advisory Section. This is the best available study for the derivation of a lifetime AADI in terms of the length of the exposure (22-24 months compared with 8 months for Goldstein et al., 1977) and the endpoints chosen (histologic examinations compared with hepatic enzyme levels).

Schwetz et al. (1978) maintained groups of 25 Sprague-Dawley rats of each sex on diets that resulted in a dose of 0, 1, 3, 10 or 30 mg pentachlorophenol/kg bw/day for 22 (male) or 24 (female) months. At the termination of the study, observations included hematology, clinical chemistry, urinalysis, determination of organ weights, and gross and microscopic examination of tissues. At the high dose level, increased serum glutamic pyruvic transaminase (SGPT) activity and pigmentation of the liver and kidney were observed in both males and females. Decreased body weight and increased urine specific gravity were observed only in the females. At a dose of 10 mg/kg bw/day, pigmentation of the liver and kidneys was observed in the

TABLE VIII-3

Effects of Long-Term Exposure to Purified Pentachlorophenol

Route	Duration of Exposure	Dose (mg/kg bw/day)	Severity Level	Effects	Reference
Oral	8 months	5	NOEL	No increase in glucuronyl transferase activity or decreased body weight.	Goldstein et al., 1977
		25	LOAEL	Increased glucuronyl transferase activity and decreased body weight.	
Oral	22-24 months	3	NOEL	No histologic alterations of the liver or kidney.	Schwetz et al., 1978
		10	LOAEL	Pigment formation in liver and kidneys of females.	
		30	AEL	Pigment formation in the liver of males and females, and kidneys of females. Decreased body weight of females. Increased urine specific gravity in females. Increased serum glutamic pyruvic transaminase activity in males and females.	
s.c.	40 weeks	6	NOAEL	Transient alteration in blood cell counts.	Catilina et al., 1981

females, but not in the males. Schwetz et al. (1978) concluded that adverse effects were not observed in their 2-year chronic feeding study at dose levels of 10 mg/kg/day in male rats and 3 mg/kg/day in female rats.

Quantification of Noncarcinogenic Effects

1-Day Health Advisory. The study by Nishimura et al. (1982) with a NOEL of 10 mg/kg/day based on liver effects is preferred for calculating a 1-day HA. Using the NOEL of 10 mg/kg bw/day derived from the study of Nishimura et al. (1982) and an uncertainty factor (UF) of 100 for an animal NOEL, a 1-day HA may be derived as follows:

$$HA = (Dose \times bw) \div (UF \times WC)$$

where

bw = body weight, 70 kg for adult
10 kg for child

WC = water consumption, 2 ℓ for adult
1 ℓ for child.

Thus, for a 70 kg adult the 1-day HA is as follows:

$$\text{1-day HA} = (10 \text{ mg/kg/day} \times 70 \text{ kg}) \div (100 \times 2 \text{ ℓ/day})$$
$$= 3.5 \text{ mg/ℓ}.$$

This HA is equivalent to 7.0 mg/day or 0.10 mg/kg bw/day.

For a 10 kg child the 1-day HA is as follows:

$$\text{1-day HA} = (10 \text{ mg/kg/day} \times 10 \text{ kg}) \div (100 \times 1 \text{ ℓ/day})$$
$$= 1.0 \text{ mg/ℓ}.$$

This HA is equivalent to 1.0 mg/day or 0.10 mg/kg bw/day.

10-day Health Advisory. The NOEL of 3 mg/kg/day found in the studies by Johnson et al. (1973) and Schwetz et al. (1978) is preferred for calculating a 10-day HA. Using an uncertainty factor of 100 for an animal NOEL, a 10-day HA may be derived.

For a 70 kg adult the 10-day HA is as follows:

$$\text{10-day HA} = (3\ \text{mg/kg/day} \times 70\ \text{kg}) \div (100 \times 2\ \text{ℓ/day}) \sim 1.1\ \text{mg/ℓ}.$$

This HA is equivalent to 2.1 mg/day or 0.030 mg/kg bw/day.

For a 10 kg child the 10-day HA is as follows:

$$\text{10-day HA} = (3\ \text{mg/kg/day} \times 10\ \text{kg}) \div (100 \times 1\ \text{ℓ/day}) \sim 0.30\ \text{mg/ℓ}.$$

This HA is equivalent to 0.30 mg/day or 0.030 mg/kg bw/day.

These 10-day health advisories are only slightly lower than the 1-day health advisories. This is reasonable, since the pharmacokinetic data (Chapter III) indicate that pentachlorophenol does not appreciably accumulate during short-term dosing.

Lifetime Adjusted Acceptable Daily Intake (AADI). A lifetime AADI may be calculated, based on the 24-month feeding study of Schwetz et al. (1978) that resulted in a NOEL of 3 mg/kg bw/day. Using an uncertainty factor of 100 for an animal NOEL, a lifetime AADI may be calculated for a 70 kg adult:

$$\text{AADI} = (3\ \text{mg/kg/day} \times 70\ \text{kg}) \div (100 \times 2\ \text{ℓ/day}) \sim 1.1\ \text{mg/ℓ}.$$

This AADI is equivalent to an ADI of 2.1 mg/day or 0.030 mg/kg bw/day and is identical to the 10-day health advisory developed for a 70 kg adult.

Carcinogenic Effects

Data are currently available from two oral studies in which the carcinogenicity of pentachlorophenol has been assessed in rats (BRL, 1968b; Schwetz et al., 1978). Pentachlorophenol was not found to be carcinogenic in either of these studies, even though doses that produced mild signs of toxicity were used. Catilina et al. (1981) also found no evidence of carcinogenicity

in Wistar rats following s.c. administration; however, the dose level and length of exposure were limited in this study. Boutwell and Bosch (1959) also reported that pentachlorophenol is not a promotor of DMBA-induced skin carcinogenesis in Sutter mice.

Quantification of Carcinogenic Effects

Since the available carcinogenicity studies on pentachlorophenol are negative, water concentrations associated with an excess cancer risk of 10^{-4}, 10^{-5} and 10^{-6} are not calculated.

Special Considerations

Carcinogenic Contaminants. The Agency restrictions on pentachlorophenol as a wood preservative considered, with respect to health risks, the fetotoxic and reproductive effects of pentachlorophenol and the oncogenic risk from the HCDD and hexachlorobenzene contaminants. Although commercial pentachlorophenol contains residues of HCDD and other dioxins, the AADI is based upon pentachlorophenol itself since the migration of the dioxins which are virtually insoluble in water would be considerably less than pentachlorophenol. Please note that TCDD has not been found to be a contaminant of pentachlorophenol.

Synergistic Effects. Pentachlorophenol may alter the toxicities of other compounds by three different mechanisms: immunological effects (see Chronic and Subchronic Toxicity Section in Chapter V), enzyme induction and inhibition of sulfation (see Interactive Effects Section in Chapter VII).

Vizethum and Goerz (1979) demonstrated the induction of microsomal enzymes by pentachlorophenol. While alteration of these enzymes by pentachlorophenol has not specifically been demonstrated to alter the toxicity of other compounds, these types of alterations in enzyme activity, in general, may change the toxic potential of a wide variety of compounds.

Pentachlorophenol may also alter immune competence, thereby altering the effects of numerous challenges to the organism. The studies of Kerkvliet et al. (1982a,b) have indicated a possible enhancement of the development of splenic tumors in mice challenged with Maloney sarcoma virus transformed cells. No effect was observed on other indicators of immune function in this study.

The third way in which pentachlorophenol may alter the toxicities of other compounds involves the inhibition of cytosolic sulfotransferases (Mulder and Scholtens, 1977). Thus, compounds such as N-hydroxy-2-acetylaminofluorene, which are activated by the formation of a sulfate ester, are considerably less toxic in animals pretreated with pentachlorophenol (Meerman et al., 1980).

High Risk Subpopulations. The data from human studies were insufficient to identify a high risk subpopulation; however, limited data from animal studies indicate that neonates may be especially susceptible to the toxic effects of pentachlorophenol. Schwetz et al. (1978) cited an unpublished study by Dow Chemical Company in which the acute LD_{50} for 3- to 4-day-old rats (65 mg/kg) was less than half the LD_{50} for adult rats (~150 mg/kg). The reproductive studies of Schwetz et al. (1974, 1978) have also consistently found greater effects in rat embryos than in the dams.

Summary

The 1-day, 10-day and lifetime health advisories are summarized in Table VIII-4. The health advisories for a 70 kg adult are >1 mg/ℓ. However, Hoak (1957) has reported an odor threshold for pentachlorophenol of 857 ppb (0.857 mg/mℓ) at 30°C (86°F) and Dietz and Traud (1978) reported threshold levels of 30 µg/ℓ for taste and 1600 µg/ℓ for odor (20-22°C). It is possible, therefore, that water concentrations of pentachlorophenol that would result in levels of concern would also be unacceptable to the general population, based on organoleptic considerations. The lifetime adjusted acceptable daily intake may undergo revision when relative source contribution data are added to this document.

TABLE VIII-4

Health Advisories for Pentachlorophenol

Exposure	Health Advisory (mg/ℓ)
1-day (adult)	3.5
1-day (child)	1.0
10-day (adult)	1.1
10-day (child)	0.30
Lifetime	1.1

IX. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values for Substances in Workroom Air, 4th ed. with supplements through 1981. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. TLVs. Threshold Limit Values for Chemical Substances and Physical Agents in the Work Environment with Intended Changes for 1983. Cincinnati, OH.

Ahlborg, U.G. and K. Larsson. 1978. Metabolism of tetrachlorophenols in the rat. Arch. Toxicol. 40(1): 63-74.

Ahlborg, U.G., J.-E. Lindgren and M. Mercier. 1974. Metabolism of pentachlorophenol. Arch. Toxicol. 32: 271.

Alexander, M. and M.I.H. Aleem. 1961. Effect of chemical structure on microbial decomposition of aromatic herbicides. J. Agric. Food Chem. 9: 44-47.

Ames, B.N., J. McCann and E. Yamasaki. 1975. Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. Mutat. Res. 31(6): 347-364.

Andersen, K.J., E.G. Leighty and M.T. Takahashi. 1972. Evaluation of herbicides for possible mutagenic properties. J. Agric. Food Chem. 20(3): 649-656.

Armstrong, R.W., E.R. Eichner, D.E. Klein, et al. 1969. Pentachlorophenol poisoning in a nursery for newborn infants. II. Epidemiologic and toxicologic studies. J. Pediatr. 75(2): 317-325.

Baader, E.W. and H.J. Bauer. 1951. Industrial intoxication due to pentachlorophenol. Ind. Med. Surg. 20: 286-290.

Baker, M.D., C.I. Mayfield and W.E. Inniss. 1980. Degradation of chlorophenol in soil, sediment and water at low temperature. Water Res. 14: 1765-1771.

Ballhorn, L., T. Rozman, K. Rozman, F. Korte and H. Greim. 1981. Cholestyramine enhances fecal elimination of pentachlorophenol in rhesus monkeys. Chemosphere. 10(8): 877-888.

BCPC (British Crop Protection Council). 1977. Pesticide Manual. Basic Information on the Chemicals Used as Active Components of Pesticides, 5th ed., H. Martin and C.R. Worthing, Ed. BCPC, Worcestershire, England.

Begley, J., E.L. Reichert, M.N. Rashad and H.W. Klemmer. 1977. Association between renal function tests and pentachlorophenol exposure. Clin. Toxicol. 11: 97-106.

Bergner, H., P. Constantinidis and J.H. Martin. 1965. Industrial pentachlorophenol poisoning in Winnipeg. Can. Med. Assoc. J. 92: 448-451.

Bevenue, A., J. Wilson, L.J. Casarett and H.W. Klemmer. 1967a. A survey of pentachlorophenol content in human urine. Bull. Environ. Contam. Toxicol. 2: 319.

Bevenue, A., T.J. Haley and H.W. Klemmer. 1967b. A note on the effects of a temporary exposure of an individual to pentachlorophenol. Bull. Environ. Contam. Toxicol. 2: 293-296.

Boutwell, R.K. and K.K. Bosch. 1959. The tumor-promoting action of phenol and related compounds for mouse skin. Cancer Res. 19: 413-424.

Braun, W.H. and M.W. Sauerhoff. 1976. The pharmacokinetic profile of pentachlorophenol in monkeys. Toxicol. Appl. Pharmacol. 38: 525.

Braun, W.H., J.D. Young, G.E. Blau and P.J. Gehring. 1977. The pharmacokinetics and metabolism of pentachlorophenol in rats. Toxicol. Appl. Pharmacol. 41: 395.

Braun, W.H., G.E. Balu and M.B. Chenoweth. 1978. The metabolism/pharmacokinetics of pentachlorophenol in man, and a comparison with the rat and monkey model. Toxicol. Appl. Pharmacol. 45: 278.

BRL (Bionetics Research Laboratories). 1968a. Evaluation of the Carcinogenic, Teratogenic and Mutagenic Activities of Selected Pesticides and Industrial Chemicals. Vol. 1. Carcinogenic Study, Publ. No. NCI-DCCP-CG-1973-1-1. Prepared by BRL, Bethesda, MD, under Contract Nos. PH 43-64-57 and PH 43-67-735. National Cancer Institute, Bethesda, MD. (NTIS PB-223-159. p. 393.

BRL (Bionetics Research Laboratories). 1968b. Evaluation of the Carcinogenic, Teratogenic and Mutagenic Activities of Selected Pesticides and Industrial Chemicals. Vol. 2. Evaluation of the Teratogenic Activity of Selected Pesticides and Industrial Chemicals in Mice and Rats. Publ. No. NCI-DCCP-CG-1973-1-2. Prepared by BRL, Bethesda, MD, under Contract Nos. PH 43-64-57 and PH 43-64-735. National Cancer Institute, Bethesda, MD. NTIS PB-223-160. p. 150.

Buhler, D.R., M.E. Rasmusson and H.S. Nakaue. 1973. Occurrence of hexachlorophene and pentachlorophenol in sewage and water. Environ. Sci. Technol. 7: 929-934.

Burns, L.H., D.M. Cline and R.R. Lassiter. 1981. Exposure Analysis Modeling System (EXAMS). Prepared by Environmental Research Lab, Office of Research and Development. U.S. EPA, Athens, GA.

Buselmaier, W., G. Rohrborn and P. Propping. 1973. Comparative investigations of the mutagenicity of pesticides in mammalian test systems. Mutat. Res. 21(1): 25.

Cabral, J.R.P., F. Raitano, T. Mollner, S. Bronczyk and P. Shubik. 1979. Acute toxicity of pesticides in hamsters. Toxicol. Appl. Pharmacol. 48: A192.

Callahan, M.A., M.W. Slimak, N.W. Gabel, et al. 1979. Water-Related Environmental Fate of 129 Priority Pollutants, Vol. II. Office of Water Planning and Standards, Office of Water and Wastewater Management. U.S. EPA, Washington, DC. EPA 440/4-79-029b.

Casarett, L.J., A. Bevenue, W.L. Yauger, Jr. and S.A. Whalen. 1969. Observations on pentachlorophenol in human blood and urine. Am. Ind. Hyg. Assoc. J. 30: 360-366.

Catilina, P., A. Chamoux, M.J. Catilina and J. Champeix. 1981. Study of the pathogenic properties of substances used as wood protectives: Pentachlorophenol. Arch. Mal. Prof. Med. Trav. Secur. Soc. 42(6): 334-337. (Fre).

Chapman, J.B. and P. Robson. 1965. Pentachlorophenol poisoning from bath water. Lancet. 1: 1266-1267.

Choi, J. and A. Aomine. 1974. Adsorption of pentachlorophenol by soils. Soil Sci. Plant Nutr. (Tokyo). 20(2): 134-144. (Cited in Callahan et al., 1979)

CRC. 1973. Handbook of Chemistry and Physics, 53rd ed. CRC Press, Cleveland, OH.

Deichmann, W. 1943. The toxicity of chlorophenols for rats. Soc. Pharmacol. Exp. Fed. Proc. 2: 76-77.

Deichmann, W., W. Machle, K.V. Kitzmiller and G. Thomas. 1942. Acute and chronic effects of pentachlorophenol and sodium pentachlorophenate upon experimental animals. J. Pharmacol. Exp. Therap. 76: 104-117.

Dietz, F. and J. Traud. 1978. Geruchs-und Geschmacks-Schwellen-Konzentration von Phenolkorpera. Gas-Wasserfach. Wasser-Abwaser. 119: 318.

Dittmer, D.S., Ed. 1959. Fungicides. Vol. 5 of Handbook of Toxicology. W.B. Saunders Co., Philadelphia, PA.

Dow Chemical Co. 1969a. Antimicrobial Agents. Dowicide 2 Antimicrobial. Available from the Dow Chemical Co., Midland, MI 48640.

Dow Chemical Co. 1969b. Antimicrobial Agents. Dowicide B Antimicrobial. Available from the Dow Chemical Co., Midland, MI 48640.

Drahonovsky, J. and Z. Vacek. 1971. Dissoziations konstanten und austauscherchromatographic chlorierter phenole. Coll. Czech. Chem. Commun. 36: 3431-3440. (Cited in Callahan et al., 1979)

Exon, J.H. and L.D. Koller. 1982. Effects of transplacental exposure to chlorinated phenols. Environ. Health Perspect. 46: 137-140.

Exon, J.H. and L.D. Koller. 1983a. Alteration of transplacental carcinogenesis by chlorinated phenols. Water Chlorination: Environ. Impact Health Eff. 4(2): 1177-1188.

Exon, J.H. and L.D. Koller. 1983b. Effects of chlorinated phenols on immunity in rats. Int. J. Immunopharmacol. 5(2): 131-136. (Taken from CA 99:34101t)

Fahrig, R. 1974. Comparative Mutagenicity Studies with Pesticides. In: Chemical Carcinogenesis Essays. IARC Scientific Publ. No. 10. WHO, IARC. p. 161-181.

Fahrig, R., C.A. Nilsson and C. Rappe. 1978. Genetic activity of chlorophenols and chlorophenol impurities. In: Pentachlorophenol: Chemistry, Pharmacology and Environmental Toxicology, K.R. Rao, Ed. Plenum Press, NY. p. 325-338.

Farquharson, M.E., J.C. Gage and J. Northover. 1958. The biological action of chlorophenols. Brit. J. Pharmacol. 13: 20-24.

Fleischer, M., R. Meiss, H. Robenek, H. Themann and R. Eckard. 1980. Ultrastructural morphometric investigations on rat liver of young and adult rats after treatment with technical pentachlorophenol (PCP). Arch. Toxicol. 44(4): 243-257.

Freiter, E.R. 1979. Chlorophenols. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., NY. 5: 864-872.

Goldstein, J.A., M. Friesen, R.E. Linder, P. Hickman, J.R. Hass and H. Bergman. 1977. Effects of pentachlorophenol on hepatic drug-metabolizing enzymes and porphyria related to contamination with chlorinated dibenzo-p-dioxins and dibenzofurans. Biochem. Pharmacol. 26: 1549-1557.

Golumbic, C. 1953. Phenol and phenols. In: Kirk-Othmer Encyclopedia of Chemical Technology, 1st ed. Interscience Publishers Inc., NY. p. 319-320.

Gordon, D. 1956. How dangerous is pentachlorophenol? Med. J. Australia. 43(2): 485-488.

Gotz, R., L.R. Schwarz and H. Greim. 1980. Effects of pentachlorophenol and 2,4,6-trichlorophenol on the disposition of sulfobromophthalein and respiration of isolated liver cells. Arch. Toxicol. 44(1-3): 147-155.

Greichus, Y.A., G.W. Libal and D.D. Johnson. 1979. Diagnosis and physiologic effects of pentachlorophenols on young pigs. Part I. Effects of purified pentachlorophenol. Bull. Environ. Contam. Toxicol. 23(3): 418-422.

Grimm, H.G., B. Schellmann, K.H. Schaller and K. Gossler. 1981. Pentachlorophenol concentrations in tissues and body fluids of normal persons. Zentralbl. Bakteriol., Mikrobiol. Hyg., Abt. 1, Orig. B. 174(1-2): 77-90. (Ger).

Hansch, C. and A.J. Leo. 1979. Substituent Constants for Correlation Analysis in Chemistry and Biology. John Wiley and Sons, Inc., NY. p. 339.

Hiatt, C.W., W.T. Haskins and L. Olivier. 1960. The action of sunlight on sodium pentachlorophenate. Am. J. Trop. Med. Hyg. 9: 527-531. (Cited in Callahan et al., 1979)

Hinkle, D.K. 1973. Fetotoxic effects of pentachlorophenol in the Golden Syrian hamster. Toxicol. Appl. Pharmacol. 25: 445.

Hoak, R.D. 1957. The causes of tastes and odors in drinking water. Water Sewage Works. 104: 243.

Hoben, H.J., S.A. Ching and L.J. Casarett. 1976. A study of inhalation of pentachlorophenol by rats. III. Inhalation toxicity study. Bull. Environ. Contam. Toxicol. 15(4): 463-465.

IARC (International Agency for Research on Cancer). 1979. Pentachlorophenol. In: Some Halogenated Hydrocarbons. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyon, France. 20: 309-325.

Jakobson, I. and S. Yllner. 1971. Metabolism of ^{14}C-pentachlorophenol in the mouse. Acta. Pharmacol. Toxicol. 29: 513.

Johnson, R.L., P.J. Gehring, R.J. Kociba and B.A. Schwetz. 1973. Chlorinated dibenzodioxins and pentachlorophenol. Environ. Health Perspect., Exp. Issue No. 5, September, 1973. p. 171.

Kerkvliet, N.I., L. Baecher-Steppan, A.T. Claycomb, A.M. Craig and G.G. Sheggeby. 1982a. Immunotoxicity of technical pentachlorophenol (PCP-T): Depressed humoral immune responses to T-dependent and T-independent antigen stimulation in PCP-T-exposed mice. Fundam. Appl. Toxicol. 2(2): 90-99. (Taken from CA 97:176334d)

Kerkvliet, N.I., L. Baecher-Steppan and J.A. Schmitz. 1982b. Immunotoxicity of pentachlorophenol (PCP): Increased susceptibility to tumor growth in adult mice fed technical PCVP-contaminated diets. Toxicol. Appl. Pharmacol. 62(1): 55-64.

Kimbrough, R.D. and R.E. Linder. 1978. The effect of technical and purified pentachlorphenol on the rat liver. Toxicol. Appl. Pharmacol. 46: 151.

Klemmer, H.W. 1972. Human health and pesticides: Community pesticide studies. Residue Rev. 41: 55-63.

Klemmer, H.W., L. Wong, M.M. Sato, E.L. Reichert, R.J. Korsak and M.N. Rashad. 1980. Clinical findings in workers exposed to pentachloropenol. Arch. Environ. Contam. Toxicol. 9(6): 715-725.

Knudsen, I., H.G. Verschuuren, E.M. Dentonkelaar, R. Kroes and P.F.W. Helleman. 1974. Short-term toxicity of pentachlorophenol in rats. Toxicology. 2(2): 141-152.

Korte, F. and W. Klein. 1982. Degradation of benzene in the environment. Ecotoxicol. Environ. Saf. 6: 311-327.

Larsen, R.V., L.E. Kirsch, S.M. Shaw, J.E. Christian and G.S. Born. 1972. Excretion and tissue distribution of uniformly labeled ^{14}C-pentachlorophenol in rats. J. Pharmacol. Sci. 61: 2004-2006.

Larsen, R.V., G.S. Born, W.V. Kessler, S.M. Shaw and D.C. VanSickle. 1975. Placental transfer and teratology of pentachlorophenol in rats. Environ. Lett. 10: 121-128.

Leighty, E.G. and A.F. Fentiman, Jr. 1982. Conjugation of pentachlorophenol to palmitic acid by liver microsomes. Bull. Environ. Contam. Toxicol. 28(3): 329-333.

Lemma, A. and B.N. Ames. 1975. Screening for mutagenic activity of some molluscicides. Trans. R. Soc. Trop. Med. Hyg. 69(1): 167-168.

Madge, D.S. 1981. The effects of pentachlorophenol on intestinal solute absorption and fluid transfer in mice. Gen. Pharmacol. 12(3): 169-175. (Taken from CA 95:36724q)

McCann, J., E. Choi, E. Yamasaki and B.N. Ames. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Natl. Acad. Sci. USA. 72(12): 5135-5139.

McGavack, T.H., L.J. Boyd, F.V. Piccione and R. Terranova. 1941. Acute and chronic intoxication with sodium pentachlorophenate in rabbits. J. Ind. Hyg. Toxicol. 23: 239.

Meerman, J.H.N. and G.J. Mulder. 1981. Prevention of the hepatotoxic action of N-hydroxy-2-acetylaminofluorene in the rat by inhibition of N-O-sulfation by pentachlorophenol. Life Sci. 28(21): 2361-2365.

Meerman, J.H.N., A.B.D. Van Doorn and G.J. Mulder. 1980. Inhibition of sulfate conjugation of N-hydroxy-2-acetylaminofluorene in isolated perfused rat liver and in the rat in vivo by pentachlorophenol and low sulfate. Cancer Res. 40(10): 3772-3779.

Meerman, J.H.N., H.M.J. Sterenborg and G.J. Mulder. 1983. Use of pentachlorophenol as long-term inhibitor of sulfation of phenols and hydroxamic acids in the rat *in vivo*. Biochem. Pharmacol. 32(10): 1587-1593.

Meister, R.T., Ed. 1972. 1972 Farm Chemicals Handbook. Meister Publishing Co., Willoughby, OH. p. C296.

Menon, J.A. 1958. Tropical hazards associated with the use of pentachlorophenol. Br. Med. J. 1: 1156-1158.

Moriya, M., T. Ohta, K. Watanabe, T. Miyazawa, K. Kato and Y. Shirasu. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat. Res. 116(3-4): 185-216.

Mulder, G.J. and E. Scholtens. 1977. Phenol sulphotransferase and uridine diphosphate glucuronyltransferase from rat liver *in vivo* and *in vitro*. Biochem. J. 65: 553-559.

NAS (National Academy of Sciences). 1977. Drinking Water and Health. VI. Organic Solutes. p. 750-753.

NIOSH (National Institute for Occupational Safety and Health). 1981. Information Profiles on Potential Occupational Hazards: Chlorophenols. Prepared by Syracuse Research Corporation under Contract No. 210-79-0030 NIOSH, Rockville, MD. p. 110-126.

Nishimura, H., N. Nishimura and H. Oshima. 1982. Effects of pentachlorophenol on the levels of hepatic glycogen. Sangyo Isaku. 24(4): 398-399.

Noakes, D.N. and D.M. Sanderson. 1969. A method for determining the dermal toxicity of pesticides. Br. J. Ind. Med. 26: 59-64.

NTP (National Toxicology Program). 1983. Chemicals on Standard Protocol. NTP, Carcinogenesis Testing Program, Bethesda, MD. Available from Technical Information Resources Branch, Carcinogenesis Testing Program, NTP, Landow Bldg., Rm. A306, Bethesda, MD 20014.

Pierce, R.H., Jr. 1978. Fate and impact of pentachlorophenol in a freshwater ecosystem. U.S. Environmental Protection Agency, (ERL), Athens, GA. p. 61. EPA 600/3-78-063. (Cited in Callahan et al., 1979)

Pierce, R.H., Jr. and D.M. Victor. 1978. The fate of pentachlorophenol in an aquatic ecosystem. p. 41-52. In: Pentachlorophenol: Chemistry, Pharmacology and Environmental Toxicology, K.R. Rao, Ed. Plenum Press, NY. p. 402. (Cited in Callahan et al., 1979)

Robson, A.M., J.M. Kissane, N.H. Elvick and L. Pundavela. 1969. Pentachlorophenol poisoning in a nursery for newborn infants. I. Clinical features and treatment. J. Pediatr. 75: 309-316.

Rott, B., R. Viswanathan, D. Freitag and F. Korte. 1982. Comparison of the applicability of various tests for screening the degradability of environmental chemicals. Chemosphere. 11: 531-538.

Rozman, T., L. Ballhorn, K. Rozman, C. Klaassen and H. Greim. 1982. Effect of cholestyramine on the disposition of pentachlorophenol in rhesus monkey. J. Toxicol. Environ. Health. 10(2): 277-283.

Schefer, W. and O. Waelchli. 1980. Testing of the biological degradability of organic chemical wastewater components. Z. Wasser. Abwasser Forsch. 13: 205-209.

Schwetz, B.A. and P.J. Gehring. 1973. The effect of tetrachlorophenol and pentachlorophenol on rat embryonal and fetal development. Toxicol. Appl. Pharmacol. 25: 455.

Schwetz, B.A., P.A. Keeler and P.J. Gehring. 1974a. The effect of purified and commercial grade tetrachlorophenol on rat embryonal and fetal development. Toxicol. Appl. Pharmacol. 28: 146-150.

Schwetz, B.A., P.A. Keeler and P.J. Gehring. 1974b. The effect of purified and commercial grade pentachlorophenol on rat embryonal and fetal development. Toxicol. Appl. Pharmacol. 28: 151-161.

Schwetz, B.A., J.F. Quast, P.A. Keeler, C.G. Humiston and R.J. Kociba. 1978. Results of 2-year toxicity and reproduction studies on pentachlorophenol in rats. In: Pentachlorophenol: Chemistry, Pharmacology and Environmental Toxicology, K.R. Rao, Ed. Plenum Press, NY. p. 301.

Shackelford, W.M. and L.H. Keith. 1976. Frequency of organic compounds identified in water. U.S. Environmental Protection Agency, (ERL), Athens, GA. p. 617. EPA 600/4-76-062.

Shirasu, Y. 1976. No title provided. J. Environ. Pollut. Control. 12: 408. (Jap).

Simmon, V.F., K. Kahanen and R.G. Tardiff. 1977. Mutagenic activity of chemicals identified in drinking water. Dev. Toxicol. Environ. Sci. 2: 249-258.

Tabak, H.H., S.A. Quave, C.I. Mashni and E.F. Barth. 1981. Biodegradability studies with organic priority pollutant compounds. J. Water Pollut. Control Fed. 53: 1503-1518.

Takahashi, W., E.R. Reichert, G.C. Fung and Y. Hukama. 1976. Acute phase proteins and pesticides exposure. Life Sci. 19: 1645.

Tullis, D.L. and F. Kadlubar. 1983. Unpublished data.

Tullis, D.L., K.M. Straub and F.F. Kadlubar. 1981. A comparison of the carcinogen-DNA adducts formed in rat liver *in vivo* after administration of single or multiple doses of N-methyl-4-aminoazobenzene. Chem.-Biol. Interact. 38: 15-27.

U.S. EPA. 1980. Ambient Water Quality Criteria for Pentachlorophenol. ECAO, U.S. EPA, Cincinnati, OH. NTIS PB 81-117764. EPA 400/4-80-065.

U.S. EPA. 1984. Position Document 4. Wood Preservative Pesticides: Creosote, Pentachlorophenol, Inorganic Arsenicals. U.S. EPA, Office of Pesticides and Toxic Substances, Washington, DC. July.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY. p. 953-954.

Vizethum, W. and G. Goerz. 1979. Induction of the hepatic microsomal and nuclear cytochrome P-450 system by hexachlorobenzene, pentachlorophenol and trichlorophenol. Chem.-Biol. Interact. 28(2-3): 291-299.

Vogel, E. and J.L. R. Chandler. 1974. Mutagenicity testing of cyclamate and some pesticides in Drosophila melanogaster. Experientia. 30: 621-623.

Waters, M.D., S.S. Sandhu, V.F. Simmon, et al. 1982. Study of pesticide genotoxicity. Basic Life Sci. 21: 275-326.

Wegman, R.C.C. and A.W.M. Hofstee. 1979. Chlorophenols in surface waters of the Netherlands (1976-1976). Water Res. 13: 651-657.

Wegman, R.C.C. and H.H. van den Broek. 1983. Chlorophenols in river sediment in the Netherlands. Water Res. 17: 227-230.

Weinbach, E.C. and J. Garbus. 1965. The interaction of uncoupling phenols with mitochondria and with mitochondrial proteins. J. Biol. Chem. 240: 1811.